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(54) Title: RETINOID-CONTAINING SUSTAINED RELEASE INTRAOCULAR DRUG DELIVERY SYSTEMS AND RELATED METHODS OF MANUFACTURING

(57) Abstract: Biocompatible intraocular implants include a retinoid component and a biodegradable polymer that is effective to facilitate release of the retinoid component into an eye for an extended period of time. The therapeutic agents of the implants may be associated with a biodegradable polymer matrix, such as a matrix that is substantially free of a polyvinyl alcohol. The implants may be placed in an eye to treat or reduce the occurrence of one or more ocular conditions, such as retinal damage, including glaucoma and proliferative vitreoretinopathy.

RETINOID-CONTAINING SUSTAINED RELEASE INTRAOCULAR DRUG DELIVERY SYSTEMS AND RELATED METHODS OF MANUFACTURING

by

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RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/567,339, filed April 30, 2004, and U.S. Provisional Application No. 60/629,928, filed November 22, 2004, the disclosures of both of which are hereby incorporated by reference in their entireties.

BACKGROUND

The present invention generally relates to devices and methods to treat an eye of a patient, and more specifically to intraocular drug delivery systems, such as implants and microparticles, that provide extended release of a therapeutic agent to an eye in which the drug delivery systems is placed, and to methods of making and using such drug delivery systems, for example, to treat or reduce one or more symptoms of an ocular condition.

Retinoid drugs exert their therapeutic activity by stimulating, blocking or inhibiting the biological activities of either or both of the retinoid-associated nuclear receptors RAR (retinoic acid receptors) and RXR (retinoid X receptors). Although not wishing to be limited by any particular theory, each of these receptors is thought to undergo a conformational change when a cognative agonist binds the receptor. This conformational change then results in the receptor stimulating or inhibiting the expression of a set of particular genes. This process is termed transactivation. In

addition, there are myriad ligand-mediated effects, such as involvement in the stimulation or mediation of cellular phosphorylation cascades, which may not be transactivational events.

Retinoid drugs formulated for oral delivery, for example, RAR agonists which affect one or more retinoic acid receptors or RARs, are currently used for the treatment of psoriasis (acitretin and etretinate) and acne (isotretinoin). These RAR agonists are known to be associated with a large diversity of side effects at the doses necessary for acceptable or substantially optimal or optimal therapeutic activity, including, without limitation, side effects similar to those commonly associated with hypervitaminosis A, metabolic and nutritional side effects, whole body side effects, endocrine side effects, hemic and lymphatic system side effects, digestive system side effects, ocular side effects, cardiovascular side effects, nervous system side effects, psychiatric side effects, typical retinoid toxicity side effects, respiratory system side effects, ear side effects, gastrointestinal tract side effects, and urinary system side effects. The side effects associated with the use of these drugs are of considerable clinical significance and often preclude the use of these drugs in many patients or necessitate the close monitoring of liver enzymes, blood chemistries, and the like.

In addition to the RAR agonists, RXR agonists, such as bexarotene, are also associated with many of the classic retinoid side effects, such as elevations of liver enzymes and blood lipids. Hypothyroidism also seems to be a relatively common feature of RXR-active retinoids and this condition is itself associated with many significant and serious complaints including mental confusion and depression.

It should be noted that RAR and RXR are each known to form dimers either between themselves (in the case of RXR-RXR homodimers) or with other receptors. Thus RXR may form dimers with receptors such as thyroid receptor (TR), vitamin D receptor and PPAR (peroxisome proliferator-activated receptor) in addition to forming a homodimer. Thus, retinoid receptor dimers may include RXR-RXR

homodimers, or heterodimers such as RXR-RAR, TXR-TR or RXR-PPAR. RAR does not appear to form homodimers and is apparently invariably paired with RXR.

The RAR and RXR receptors each has three major subtypes; thus, RAR receptors comprise RAR alpha, RAR beta, and RAR gamma. Similarly, RXR receptors comprise RXR alpha, RXR beta, and RXR gamma.

Tretinoin is an endogenous retinoid, which is metabolized readily to isotretinoin and other metabolites, including 9-cis retinoic acid. Tretinoin binds and transactivates both RAR and RXR, as does isotretinoin and 9-cis-retinoic acid. Tretinoin (Vesanoid) is used systemically for the treatment of acute promyclocytic anemia. The side effects of systemic tretinoin are typical of those accompanying systemic retinoid use generally, and appear to represent both RAR and RXR-type side effects.

Many retinoid drugs are formulated for oral delivery, for example, RAR agonists such as isotretinoin (Accutane), RXR agonists such as bexarotene (Targretin) and RAR, RXR dual agonists such as acitretin (Soriatane). For these retinoids, peak blood concentrations vary depending upon when the oral drug was administered relative to meals; however the time to peak blood concentration does not appear to be affected. In the case of isotretinoin the total dose of the drug must be more than doubled to reach the same peak blood concentration following a high fat meal as compared to the fasted state. This is seen as a significant disadvantage for these potent oral retinoids since the drug-absorption profile can drastically change depending upon the fasted or fed state of the patient.

Non-compliance with prescribed treatment regimens and oral administration directions could undermine the effectiveness of these retinoids when treating disease states, such as, without limitation, for retinal ocular conditions e.g. age related macular degeneration, diabetic neuropathy and the like. Moreover, retinoid absorption variability can lead not only to reduced therapeutic efficacy resulting from

fluctuations of therapeutic drug-blood levels, but can also cause unwarranted drug side effects due in inadvertently high tissue exposure. It is therefore important, and indeed reinforced by prescribing physicians and the US Food and Drug Administration, that oral doses of retinoids be taken with food.

Proliferative vitreoretinopathy (PVR) remains the major cause of failure in retinal reattachment surgery. The pathophysiology of PVR involves the migration, dedifferentiation, and proliferation of retinal pigmented epithelial (RPE) cells and glial cells into the vitreous followed by epiretinal membrane formation. Contraction of the cellular membrane leads to the breakdown of the blood-retinal barrier and traction retinal detachment.

The onset of PVR is heralded by the migration of RPE cells into the vitreous. RPE dedifferentiation and proliferation occurs in PVR, proliferative diabetic retinopathy (PDR) and choroidal neovascularization. Several growth factors and cytokines have been implicated in the proliferative process and include: aFGF, bFGF, epidermal growth factor, IGF-I, TGF-beta, interleukin 1, 6 and 8 (IL-1, IL-6,IL-6), interferon gamma (IFN gamma), epidermal growth factor, macrophage colony stimulating factor(M-CSF) and monocyte chemotactic factor-1 (MCP-1). Pharmacological treatment of PVR is generally aimed at downstream sequelae of RPE proliferation, specifically membrane formation and inflammatory infiltration. This includes the use of corticosteroids to prevent the inflammatory component and macrophage recruitment and cytostatics to prevent the proliferative phase. Triamcinolone acetonide and dexamethasone have both been studied to prevent traction retinal detachment from PVR. The corticosteroids are to some degree effective but carry significant side effects including cataract formation and elevation of IOP. Numerous cytostatic agents have also been examined and include: cytarabine, 5-fluorouracil, duanorubicin, aclacinomycin A, BCNU, N,N dimethyladriamycin, and taxol. These agents have been shown to inhibit traction retinal detachment in animal models of PVR but carry significant side effects ranging from retinal disruption to carcinogenicity.

The use of retinoic acid (RA) and other retinoids has been investigated and show promise in fulfilling the PVR treatment needs. Retinoids treat the underlying pathology of PVR, RPE dedifferentiation and proliferation, as well as the downstream effects. Retinoids have an antiproliferative effect on epithelial, mesenchymal and neoplastic cells. All trans-retinoic acid (RA) is known to inhibit retinal pigmented epithelial proliferation. It has also been suggested that retinoids might be able to enhance density-dependent growth regulation in RPE. Studies have shown that RA prevents RPE proliferation in-vitro in a biphasic manner with IC_{50} of 10 pM and 17 nM. Retinoic acid also inhibits human RPE expression of stromelysin. It is believed that this prevents the cleaving of proteins in the extracellular space that leads to RPE dispersion. Additionally, RA has been shown to modulate the effect of bFGF in cultured RPE cells. RA inhibited bFGF stimulated RPE proliferation. Scatchard plot analysis suggested that RA decreased the number of bFGF binding sites on the RPE cells. Recycling of retinoids is required for maintenance of normal visual function as they play an important role in visual transduction. The lack of retinoid input could contribute to RPE dedifferentiation, migration, and proliferation processes that occur after retinal detachment and where PVR has been previously been involved results in poor return of vision after retinal reattachment.

Animal models of PVR have demonstrated the relative safety and efficacy of retinoids in the prevention of traction retinal detachment. Ten and 15 μg of RA in 1-% hyaluronic acid and BSS reduced traction retinal detachment in an animal model of PVR. Five to ten μg of RA and 13-*cis*-retinoic acid in a silicone oil tamponade have both been shown to effectively prevent traction retinal detachment. Histopathology and ophthalmoscopic examination indicated no ocular toxicity associated with this dose of RA. Additional studies have shown that RA concentrations up to 15 μg/mL are well tolerated with no ERG changes. The beneficial effects of retinoids in the prevention of PVR have also been shown in

humans. Orally administered 13-cis-retinoic acid was effective at decreasing PVR and increasing the rate of retinal attachment in a retrospective study.

Age Related Macular Degeneration is the leading cause of blindness for individuals greater than fifty years old. The disease is heralded by the formation of focal yellow-gray lesions in Bruch's membrane. The RPE phenotype changes result in a dysregulation of the extracellular matrix synthesis and degradation. The lesions, drusen, are comprised of lipid-rich extracellular matrix components and may coalesce overtime resulting in a shallow elevation of the RPE cells. The RPE cells begin to clump, aggregate and atrophy. Degeneration of the RPE cells leads to a secondary degeneration of the overlying photoreceptors.

Retinoids may alter the phenotype of the RPE cells. Restoring RPE cell function, ECM metabolism and the intimate relationship between the RPE and photoreceptors. In addition to the RPE effects, tazarotene appears to be retinal protective in a light degeneration animal model.

Retinoids have also been shown to be effective in Stargardt's disease and to improve neural survival in rhodopsin mutant transgenic mice as well as light.

Degeneration of retinal neurons is a major cause of blindness. In glaucoma, ganglion cell death is the direct cause of blindness. In retinal degenerative disorders, including retinitis pigmentosa and age-related macular degeneration, photoreceptor death results in loss of vision. Although currently there is no effective treatment to prevent degeneration in retinal neurons, recent demonstration that retinal neurons are protected by various neurotrophic factors and small molecules indicates that pharmacological therapies for these conditions are a possibility.

In treating ocular conditions, it is important to keep in mind that the internal structures of the eye are sequestered from the general circulation of a patient by a series of highly selective barriers. These barriers prevent the rapid equilibration of

compounds in the plasma with the tissues of the eye. The anatomy and physiology of the eye gives rise to the concept of the blood-aqueous and the blood-retinal barriers. Collectively these are known as the blood ocular barriers.

Access to the aqueous humor of the anterior and posterior chambers is restricted by the blood-aqueous barrier. The aqueous humor is not a simple ultrafiltrate of the blood and has a composition resulting from the combined actions of the secretory activity in the ciliary processes and the selectivity of the blood aqueous barrier. The nonpigmented cells of the ciliary body line the posterior chamber and represent part of the blood-aqueous barrier. The tight junctions joining the membranes of the cells, however, are not completely belted and this discontinuity results in intercellular pores through which solutes of intermediate size may diffuse.

The endothelial cells of the iris vessels comprise the remainder of the blood aqueous barrier. However, the cells lining the anterior surface of the iris stroma have numerous openings and present very little barrier in accessing the anterior chamber. Compounds administered systemically will penetrate the leaky vessels of the ciliary body and diffuse through the iris into the anterior chamber aqueous humor. Movement into the posterior chamber from the anterior chamber is restricted by the diaphragm like action of the iris on the lens. Many lipophilic substances such as chloramphenecol and tetracycline may penetrate readily across the blood-aqueous barrier into the posterior chamber.

The systemic administration of compounds that gain access to the vitreous via the posterior chamber is extremely inefficient. Drug must diffuse from the posterior chamber into the deeper segments of the vitreous body while competing with the parallel elimination of the posterior aqueous humor through the anterior chamber and the normal aqueous humor egress pathways. Compounds diffusing into the vitreous from the posterior chamber will develop a concentration gradient

across the vitreous. This concentration gradient, however, is shallow and rapidly reversed as the aqueous humor concentration falls.

Penetration of drugs directly into the posterior segment of the eye is restricted by the blood-retinal barriers. The blood-retinal barrier is anatomically separated into an inner and outer blood barriers. The choroid lies immediately inside the sclera and is the most vascularised tissue of the posterior globe. Numerous fenestrae are present in the endothelium of the chorioapillaries resulting in very little resistance to the transport of systemic solutes into the choroid. Systemically administered compounds penetrate into the choroid in a matter of minutes and the choroid rapidly equilibrates with the plasma. Further movement of systemically borne solutes into the internal ocular structures from the choroid is restricted by the retinal pigmented epithelium (RPE). The cells of this structure are joined by zonulae ocludentae intercellular junctions. The RPE is a "tight" ion transporting barrier a paracellular transport of solutes across the RPE is restricted.

The endothelium of the retinal vessels represents the inner blood-retinal barrier. The endothelial cells of the retinal vessels are completely banded by zonulae occludentae junctions preventing the paracellular transport of most blood solutes. The retinal vessels are similar to the vessels in the brain that comprise the blood-brain barrier in that the are very impermeable. The permeability of most compounds across the blood-retinal barriers is very low. Extremely lipophilic compounds, however, such as chloramphenicol and benzyl penicillin can penetrate the blood-retinal barrier achieving appreciable concentrations in the vitreous humor after systemic administration.

The lipophilicity of the compound correlates with its rate of penetration and is consistent with passive cellular diffusion. The blood retinal barrier, however, is impermeable to polar or charged compounds in the absence of a transport mechanism.

Thus, delivery of drugs to the retina, vitreous and uveal tract is typically achieved by high systemic dosing or direct intra-ocular injections.

Tazarotene, ethyl 6-[4,4-dimethylthiochroman-6-yl) ethyl] nicotinate, is a proprietary acetylenic retinoid compound developed by Allergan for psoriasis and acne vulgaris. Tazarotene is an ethyl ester prodrug that is metabolized to its active form, tazarotenic acid, by rapid deesterification in animals and human. Tazarotenic acid mediates its responses primarily through activation of nuclear retinoid receptors and has been proven to be pharmacologically active in tests using proliferative vitreoretinopathy (PVR) animal models.

The use of the retinoid. Tazarotene, is discussed in the following references: Drugs Future 28(2):208-09 (2003); Marks, "Topical tazarotene: review and re-evaluation", Retinoids, 17(3):72-74 (2001); Phillips et al., "Efficacy of 0.1% tazarotene cream for the treatment of photodamage", Arch Dermatol, 138(11):1486-1493 (2002); Guenther, "Optimizing treatment with topical tazarotene", Am J Clin Dermatol, 4(3):197-202 (2003).

U.S. Patent No. 6,713,081 discloses ocular implant devices made from polyvinyl alcohol and used for the delivery of a therapeutic agent to an eye in a controlled and sustained manner. The implants may be placed subconjunctivally or intravitreally in an eye.

Biocompatible implants for placement in the eye have also been disclosed in a number of patents, such as U.S. Pat. Nos. 4,521,210; 4,853,224; 4,997,652; 5,164,188; 5,443,505; 5,501,856; 5,766,242; 5,824,072; 5,869,079; 6,074,661; 6,331,313; 6,369,116; and 6,699,493.

It would be advantageous to provide eye implantable drug delivery systems, such as intraocular implants, and methods of using such systems, that are capable

of releasing a therapeutic agent at a sustained or controlled rate for extended periods of time and in amounts with few or no negative side effects.

SUMMARY

The present invention provides new drug delivery systems, and methods of making and using such systems, for extended or sustained drug release into an eye, for example, to achieve one or more desired therapeutic effects. The drug delivery systems can be in the form of implants or implant elements, or microparticles that may be placed in an eye. The present systems and methods advantageously provide for extended release times of one or more therapeutic agents. Thus, the patient in whose eye the drug delivery has been placed receives a therapeutic amount of an agent for a long or extended time period without requiring additional administrations of the agent. For example, the patient has a substantially consistent level of therapeutically active agent available for consistent treatment of the eye over a relatively long period of time, for example, on the order of at least about one week, such as between about one and about six months after receiving an implant or microparticles. Such extended release times facilitate obtaining successful treatment results. The sustained local delivery of the therapeutic agent from the present systems reduces the high transient concentrations associated with pulsed dosing. Furthermore, direct intravitreal administration of the present systems obviates the constraints posed by the blood-retinal barrier and significantly reduces the risk of systemic toxicity.

Intraocular drug delivery systems, including implants and microparticles, in accordance with the disclosure herein comprise a therapeutic component and a drug release sustaining component associated with the therapeutic component. In accordance with the present invention, the therapeutic component comprises, consists essentially of, or consists of, a retinoid component. For example, the therapeutic component may comprise, consist essentially of, or consist of, one or

more RAR or RXR agonists, such as tazarotenic acid, or a prodrug of an RAR or RXR agonists, such as tazarotene, and the like.

A prodrug is an inactive derivative of a known active drug with enhanced delivery characteristics and therapeutic value. It is converted back to the parent compound by virtue of its enzymatic and/or chemical lability within the biologic system. The present systems may include therapeutic agents whose target tissue is in the posterior of the eye. The functional groups of the parent compound amenable to prodrug derivatization can include carboxylic acids, hydroxyl groups, amine groups or any other functionality known to be amenable to prodrug derivatization. Prodrugs include esters of hydroxyl containing groups. Other prodrugs of hydroxyl containing compounds include phosphate esters, hemiesters of dicarboxylic acids, acyloxyalkyl and ethers. Prodrugs of the amine functionality include N-Mannich Bases and Amides.

The drug release sustaining component is associated with the therapeutic component to sustain release of an amount of the retinoid component into an eye in which the drug delivery system is placed. The amount of the retinoid component is released into the eye for a period of time greater than about one week after the system is placed in the eye and is effective in reducing or treating an ocular condition, such as proliferative vitreal retinopathy, age related macular degeneration, diabetic retinopathy and retinitis pigmentosa, among others.

In one embodiment, intraocular drug delivery systems comprise a retinoid component and a biodegradable polymer matrix. The retinoid component is associated with a biodegradable polymer matrix that degrades at a rate effective to sustain release of an amount of the retinoid component from the system effective to treat an ocular condition. The intraocular drug delivery system is biodegradable or bioerodible and provides a sustained release of the retinoid component in an eye for extended periods of time, such as for more than one week, for example for about one month or more and up to about six months or more. The drug delivery system

may include one or more intravitreal implants, or one or more intravitreal microparticles, or combinations thereof.

Retinoids of the present systems may be capable of activating or enhancing the activity of an RARα, an RARβ, an RARγ, an RXRα, an RXRβ, or an RXRγ. In certain systems, the retinoid component is a hydrophilic compound, for example, the retinoid may have a log partition coefficient (log P) of less than about 3.0. In certain systems, the retinoid component is tazarotenic acid, a prodrug of tazarotenic acid, salts thereof, and mixtures thereof.

The biodegradable polymer matrix of the foregoing systems may be a mixture of biodegradable polymers or the matrix may comprise a single type of biodegradable polymer. For example, the matrix may comprise a polymer selected from the group consisting of polylactides, poly (lactide-co-glycolides), polycaprolactones, and combinations thereof.

A method of making the present systems involves combining or mixing the retinoid component with a biodegradable polymer or polymers. The mixture may then be extruded or compressed to form a single composition. The single composition may then be processed to form individual implants suitable for placement in an eye of a patient. Another method may involve an emulsion/solvent extraction process, which may be useful in producing polymeric microparticles.

Other implants may comprise a therapeutic component, which comprises, consists essentially of, or consists of a retinoid component, and a drug release sustaining component which includes a non-biodegradable polymer, such as a coating with one or more orifices or holes, such as the implants disclosed in U.S. Pat. No. 6,331,313.

Additional systems may comprise a drug release sustaining component that comprises a hydrogel.

The drug delivery systems may be placed in an ocular region to treat a variety of ocular conditions, such as treating, preventing, or reducing at least one symptom associated with an ocular condition, including without limitation, proliferative vitreal retinopathy, age related macular degeneration, diabetic retinopathy and retinitis pigementosa.

Kits in accordance with the present invention may comprise one or more of the present drug delivery systems, and instructions for using the systems. For example, the instructions may explain how to administer the implants to a patient, and types of conditions that may be treated with the implants.

Each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present invention provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention.

Additional aspects and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying drawings and examples.

Drawings

Figure 1A is a graph illustrating the release of tazarotene from PLA microspheres. The graph depicts three separate release studies of the same sample.

Figure 1B is a graph illustrating the release of tazarotene from PLGA microspheres. The graph depicts three separate release studies of the same sample.

Figure 2 is a graph illustrating in-vitro release of tazarotenic acid from poly (lactic acid), PLA, and poly (lactide-co-glycolide) implants into PBS, pH 7.4.

Figure 3 is a graph illustrating tazarotene concentration (mean + SD) in aqueous humor, vitreous humor, and retina (N = 4) after a single subconjunctival injection of 1 mg tazarotene in a suspension.

Figure 4 is a graph illustrating tazarotenic acid concentration (mean + SD) in aqueous humor, vitreous humor, and retina (N = 4) after a single subconjunctival injection of 1 mg tazarotene in a suspension.

Figure 5 is a graph illustrating tazarotene concentration (mean + SD) in aqueous humor, vitreous humor, and retina (N = 4) after a single subconjunctival injection of 1 mg tazarotene in a solution.

Figure 6 is a graph illustrating tazarotenic acid concentration (mean + SD) in aqueous humor, vitreous humor, and retina (N = 4) after a single subconjunctival injection of 1 mg tazarotene in a solution.

Figure 7 is a graph illustrating tazarotene concentration (mean + SD) in aqueous humor, vitreous humor, and retina (N = 4) after a single subconjunctival injection of 0.5 mg tazarotene in PLGA microspheres.

Figure 8 is a graph illustrating tazarotenic acid concentration (mean + SD) in aqueous humor, vitreous humor, and retina (N = 4) after a single subconjunctival injection of 0.5 mg tazarotene in PLGA microspheres.

Figure 9 is a graph illustrating intravitreal concentrations of tazarotene and tazarotenic acid following Intravitreal administration of tazarotene

Figure 10 is a graph illustrating vitreous tazarotene/ tazarotenic acid concentration ratios: 1. Subcinjunctival Suspension, 2. Subcinjunctival Oil, 3. Subcinjunctival Microsphere, 4. Intravitreal Injection

Figure 11 is a graph illustrating tissue-to-plasma concentration ratios of after twenty-one days of daily topical application of 14C-tazarotene to the skin of rats.

Figure 12 is a graph illustrating tazarotene retinal/ vitreous ratios after intraocular and subconjunctival administration: 1. Intravitreal Injection 2. Subconjunctival Suspension, 3. Subconjunctival Oil, 4. Subconjunctival Microspheres

Figure 15A is a graph illustrating tazarotene release profiles - RG502H (0.5% Tween-80 / Saline, 37 °C, n = 3).

Figure 15B is a graph illustrating tazarotene release profiles – RG502 (0.5% Tween-80 / Saline, 37 °C, n = 3).

Figure 15C is a graph illustrating tazarotene release profiles – RG752 (0.5% Tween-80 / Saline, 37 °C, n = 3).

Figure 15D is a graph illustrating tazarotene release profiles - R202H (0.5% Tween-80 / Saline 37, °C, n = 3)

Figure 16 is a graph illustrating tazarotene release profile of formulation 1, 4, 9, 17, 18, and 19 (500 μg dose, n = 3, 37 °C)

Figure 17 is a graph illustrating tazarotene release of formulation 1, 9, 12, and 17 (500 μg dose, n = 3, 37 °C)

Figure 18 is a graph illustrating tazarotene release profile of GLP Lot # 229-01 (500 μg dose, 37 °C, n = 6).

Figure 19 is a graph illustrating tazarotene release profiles – 50 μg dose (0.5% Tween-80 / Saline, 37 °C, n =6)

Figure 20 is a graph illustrating tazarotene release profiles – 50 μg dose (0.5% Tween-80 / Saline, 37 °C, n =6)

Figure 21 is a graph illustrating tazarotene release profile – 50 μg dose (0.5% Tween-80 / Saline, 37 °C, n =6)

Figure 22 is a graph illustrating tazarotene release profile (0.5% Tween-80 / Saline, 37 °C, n = 3)

Figure 23A is a graph illustrating tazarotene release profiles with polymer blend (0.5% Tween-80 / Saline, 37 °C, n =6).

Figure 23B is a graph illustrating tazarotene release profiles with polymer blend (0.5% Tween-80 / Saline, 37 °C, n =6).

Figure 24 is a graph illustrating tazarotene wafer release profiles (0.5% Tween-80 / Saline, 37 °C, n = 6)

Figure 25 is a graph illustrating tazarotene release profile from microspheres.

Figure 26 is a graph illustrating tazarotenic acid concentration (mean ± SEM) in aqueous humor (upper graph) and lens (lower graph) (N = 4) after a single intravitreal implantation of Formulation #1, #9, and #12 containing 500 µg tazarotene.

Figure 27 is a graph illustrating tazarotenic acid concentration (mean ± SEM) in retina (upper graph) and vitreous humor (lower graph) (N = 4) after a single

intravitreal implantation of Formulation #1, #9, and #12 containing 500 μg tazarotene.

Figure 28 is a graph illustrating tazarotenic acid concentration (mean ± SEM) in plasma (N = 2) after a single intravitreal implantation of Formulation #1, #9, and #12 containing 500 μg tazarotene.

Figure 29 is a graph of tazarotenic acid and tazarotene concentrations in the vitreous humor, retina, and plasma from tazarotene intravitreal implants.

Figure 30 is a graph of tazarotenic acid and tazarotene concentrations in the vitreous humor, retina, and plasma from tazarotene subconjunctival implants.

Figure 31 is a graph of Fastenberg results from PVR implants.

Figure 32 provides photographs showing differences in polymer-containing compositions that have been oven dried or freeze dried.

Figure 33 provides graphs and photographs illustrating the effects of gamma sterilization on microparticle volume size. The left panel is before gamma sterilization and the right panel is after gamma sterilization.

Figure 34 is a graph of microparticle volume distribution of non-sterile and sterile microparticles that were sterilized at reduced temperatures.

Figure 35 is a flow chart of one method of producing polymeric drug delivery systems containing a retinoid component.

Figure 36 provides photographs showing effects of sterilization for different batches of microparticles containing different amounts of a retinoid component and different polymers.

Figure 37 provides graphs showing dissolution profiles for three different retinoids (top panels, middle panels, and bottom panels) at different amounts and different polymers.

Figure 38 provides photographs of one batch of microparticles (DL003) after one month of storage at 40 C, at 20x (left panel), 60x (middle panel), and 100x (right panel) magnifications. Microparticle aggregates are observed.

Figure 39 provides photographs of an example of a batch of microparticles after two months of storage at 25, 30, or 40 C. Irregular shapes of microparticles are observed.

Figure 40 provides graphs of dissolution profiles for tazarotene-containing microspheres that were stored at 25, 30, or 40 C.

Figure 41 provides graphs of dissolution profiles for tazarotene-containing microspheres stored at different temperatures, and containing different amounts of tazarotene and/or polymers.

Figure 42 provides graphs of dissolution profiles for batch DL003 observed at 44 days.

Figure 43 provides graphs of dissolution profiles for batches DL005, DL006, DL009, and DL010 observed at 252 days.

Figure 44 provides electron microscopic photographs of microparticles containing 10% tazarotene (left panel) or 20% tazarotene (right panel).

Figure 45 provides electron microscopic photographs showing the effects of gamma sterilization on microparticles containing 10% tazarotene.

Figure 46 provides electron microscopic photographs showing microparticle appearance after 21 days (left panel) and 45 days (right panel) of dissolution.

DESCRIPTION

As described herein, controlled and sustained administration of a therapeutic agent through the use of one or more intraocular drug delivery systems, such as implants and microparticles, may improve treatment of undesirable ocular conditions. The systems comprise a pharmaceutically acceptable polymeric composition and are formulated to release one or more pharmaceutically active agents, such as retinoids, such as RAR or RXR agonists, or retinoid precursors, over an extended period of time. The systems are effective to provide a therapeutically effective dosage of the agent or agents directly to a region of the eye to treat, prevent, and/or reduce one or more symptoms of one or more undesirable ocular conditions. Thus, with a single administration, therapeutic agents will be made available at the site where they are needed and will be maintained for an extended period of time, rather than subjecting the patient to repeated injections or, in the case of self-administered drops, ineffective treatment with only limited bursts of exposure to the active agent or agents or, in the case of systemic administration, higher systemic exposure and concomitant side effects or, in the case of non-sustained release dosages, potentially toxic transient high tissue concentrations associated with pulsed, non-sustained release dosing.

An intraocular drug delivery system in accordance with the disclosure herein comprises a therapeutic component and a drug release sustaining component associated with the therapeutic component. In accordance with the present invention, the therapeutic component comprises, consists essentially of, or consists of, a retinoid component, such as a RAR agonist or a RXR agonist, or a RAR agonist precursor or prodrug, or a RXR agonist precursor or prodrug. The drug release sustaining component is associated with the therapeutic component to

sustain release of an effective amount of the therapeutic component into an eye in which the system is placed. The amount of the therapeutic component is released into the eye for a period of time greater than about one week after the system is placed in the eye, and is effective in treating and/or reducing at least one symptom of one or more ocular conditions, such as proliferative vitreal retinopathy, age related macular degeneration, diabetic retinopathy and retinitis pigementosa, and the like.

Definitions

For the purposes of this description, we use the following terms as defined in this section, unless the context of the word indicates a different meaning.

As used herein, a "drug delivery system" refers to one or more devices or elements that include at least one therapeutic agent or active ingredient and is configured to be placed in an eye. Drug delivery systems include intraocular implants and microparticles. Microparticles are elements that are smaller than intraocular implants.

As used herein, an "intraocular implant" refers to a device or element that is structured, sized, or otherwise configured to be placed in an eye. Intraocular implants are generally biocompatible with physiological conditions of an eye and do not cause unacceptable adverse side effects. Intraocular implants may be placed in an eye without disrupting vision of the eye.

As used herein, a "therapeutic component" refers to a portion of an intraocular drug delivery system comprising one or more therapeutic agents or substances used to treat a medical condition of the eye. The therapeutic component may be a discrete region of an intraocular implant, or it may be homogenously distributed throughout the implant. The therapeutic agents of the therapeutic component are typically ophthalmically acceptable, and are provided in a form that does not cause adverse reactions when the system is placed in an eye.

As used herein, a "drug release sustaining component" refers to a portion of the intraocular drug delivery system that is effective to provide a sustained release of the therapeutic agents of the system. A drug release sustaining component may be a biodegradable polymer matrix, or it may be a coating covering a core region of the system that comprises a therapeutic component.

As used herein, "associated with" means mixed with, dispersed within, coupled to, covering, or surrounding.

As used herein, an "ocular region" or "ocular site" refers generally to any area of the eyeball, including the anterior and posterior segment of the eye, and which generally includes, but is not limited to, any functional (e.g., for vision) or structural tissues found in the eyeball, or tissues or cellular layers that partly or completely line the interior or exterior of the eyeball. Specific examples of areas of the eyeball in an ocular region include the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

As used herein, an "ocular condition" is a disease, ailment or condition which affects or involves the eye or one of the parts or regions of the eye. Broadly speaking the eye includes the eyeball and the tissues and fluids which constitute the eyeball, the periocular muscles (such as the oblique and rectus muscles) and the portion of the optic nerve which is within or adjacent to the eyeball.

An anterior ocular condition is a disease, ailment or condition which affects or which involves an anterior (i.e. front of the eye) ocular region or site, such as a periocular muscle, an eye lid or an eye ball tissue or fluid which is located anterior to the posterior wall of the lens capsule or ciliary muscles. Thus, an anterior ocular condition primarily affects or involves the conjunctiva, the cornea, the anterior

chamber, the iris, the posterior chamber (behind the iris but in front of the posterior wall of the lens capsule), the lens or the lens capsule and blood vessels and nerve which vascularize or innervate an anterior ocular region or site.

Thus, an anterior ocular condition can include a disease, ailment or condition, such as for example, aphakia; pseudophakia; astigmatism; blepharospasm; cataract; conjunctival diseases; conjunctivitis; corneal diseases;, corneal ulcer; dry eye syndromes; eyelid diseases; lacrimal apparatus diseases; lacrimal duct obstruction; myopia; presbyopia; pupil disorders; refractive disorders and strabismus. Glaucoma can also be considered to be an anterior ocular condition because a clinical goal of glaucoma treatment can be to reduce a hypertension of aqueous fluid in the anterior chamber of the eye (i.e. reduce intraocular pressure).

A posterior ocular condition is a disease, ailment or condition which primarily affects or involves a posterior ocular region or site such as choroid or sclera (in a position posterior to a plane through the posterior wall of the lens capsule), vitreous, vitreous chamber, retina, retinal pigmented epithelium, Bruch's membrane, optic nerve (i.e. the optic disc), and blood vessels and nerves which vascularize or innervate a posterior ocular region or site.

Thus, a posterior ocular condition can include a disease, ailment or condition, such as for example, acute macular neuroretinopathy; Behcet's disease; choroidal neovascularization; diabetic uveitis; histoplasmosis; infections, such as fungal or viral-caused infections; macular degeneration, such as acute macular degeneration, non-exudative age related macular degeneration and exudative age related macular degeneration; edema, such as macular edema, cystoid macular edema and diabetic macular edema; multifocal choroiditis; ocular trauma which affects a posterior ocular site or location; ocular tumors; retinal disorders, such as central retinal vein occlusion, diabetic retinopathy (including proliferative diabetic retinopathy), proliferative vitreoretinopathy (PVR), retinal arterial occlusive disease, retinal detachment, uveitic retinal disease; sympathetic opthalmia; Vogt Koyanagi-Harada

(VKH) syndrome; uveal diffusion; a posterior ocular condition caused by or influenced by an ocular laser treatment; posterior ocular conditions caused by or influenced by a photodynamic therapy, photocoagulation, radiation retinopathy, epiretinal membrane disorders, branch retinal vein occlusion, anterior ischemic optic neuropathy, non-retinopathy diabetic retinal dysfunction, retinitis pigmentosa, and glaucoma. Glaucoma can be considered a posterior ocular condition because the therapeutic goal is to prevent the loss of or reduce the occurrence of loss of vision due to damage to or loss of retinal cells or optic nerve cells (i.e. neuroprotection).

The term "biodegradable polymer" refers to a polymer or polymers which degrade in vivo, and wherein erosion of the polymer or polymers over time occurs concurrent with or subsequent to release of the therapeutic agent. Specifically, hydrogels such as methylcellulose which act to release drug through polymer swelling are specifically excluded from the term "biodegradable polymer". The terms "biodegradable" and "bioerodible" are equivalent and are used interchangeably herein. A biodegradable polymer may be a homopolymer, a copolymer, or a polymer comprising more than two different polymeric units.

The term "treat", "treating", or "treatment" as used herein, refers to reduction or resolution or prevention of an ocular condition, ocular injury or damage, or to promote healing of injured or damaged ocular tissue.

The term "therapeutically effective amount" as used herein, refers to the level or amount of agent needed to treat an ocular condition, or reduce or prevent ocular injury or damage without causing significant negative or adverse side effects to the eye or a region of the eye.

Intraocular drug delivery systems have been developed which can release drug loads over various time periods. These systems, which when inserted into an eye, such as the vitreous of an eye, provide therapeutic levels of a retinoid component, such as a RAR or RXR agonist, or precursor thereof, for extended

periods of time (e.g., for about 1 week or more). The disclosed systems are effective in treating ocular conditions, such as proliferative vitreal retinopathy, age related macular degeneration, diabetic retinopathy and retinitis pigementosa.

In one embodiment of the present invention, an intraocular drug delivery system, such as an implant or microparticle, comprises a biodegradable polymer matrix. The biodegradable polymer matrix is one type of a drug release sustaining component. The biodegradable polymer matrix is effective in forming a biodegradable intraocular drug delivery system. The biodegradable intraocular drug delivery system comprises a retinoid component associated with the biodegradable polymer matrix. The matrix degrades at a rate effective to sustain release of an amount of the retinoid component for a time greater than about one week from the time in which the system is placed in ocular region or ocular site, such as the vitreous of an eye.

The retinoid component preferably includes an active retinoid agent and/or a precursor of an active retinoid agent effective to selectively, and even specifically, affect, for example, bind to and/or activate and/or inhibit the activation of and/or block, at least one of RAR-beta and RAR-gamma relative to RAR-alpha.

As used herein, the terms "selectively" or "more selectively" refer to the ability of an active retinoid agent to affect one or more first subtype(s) of RAR relative to one or more other second subtype(s) of RAR. In preferred embodiments, the first subtype(s) is affected at least about 5, about 10, about 20, about 50, about 100, or about 1000 times more than the second subtype(s). The term "specifically" refers to the ability of an active retinoid agent to affect one or more first RAR subtype(s) without substantially affecting, or preferably without affecting in a detectable way, one or more other second RAR subtype(s).

In certain drug delivery systems, the retinoid component includes an active retinoid agent or a precursor of an active retinoid agent effective to selectively or

even specifically affect both RAR-beta and RAR-gamma relative to RAR-alpha. The retinoid component advantageously includes an active retinoid agent or a precursor of an active retinoid agent effective to selectively or even specifically activate or inhibit the activation of or block at least one or both of RAR-beta and RAR-gamma relative to RAR-alpha. In one embodiment, the retinoid component includes an active retinoid agent or a precursor of an active retinoid agent effective to selectively or even specifically activate at least one of or both RAR-beta and RAR-gamma relative to RAR-alpha.

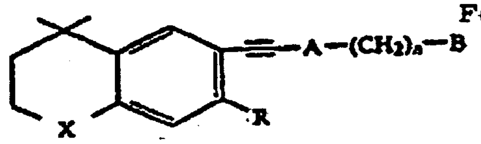
Although the present systems may comprise a large variety of retinoid components, such as active retinoid agents or precursors of active retinoid agents which have RAR-antagonist activity and RAR-inverse agonist activity, the present invention is particularly useful with retinoid components which include active retinoid agents or precursors of active retinoid agents which have RAR-agonist activity.

In certain systems, the retinoid component includes an active retinoid agent having a substantial degree of water solubility, for example, is more water soluble than isotretinoin, or is metabolically converted in the human or animal into an active retinoid agent having a substantial degree of water solubility. In this way, it is possible to avoid having the retinoid cross lipid barriers, such as the blood brain barrier and the retinal-blood barrier. This specifically avoids some of the usual adverse side effects of other retinoids, such as central nervous system (CNS) effects and eye toxicities.

The retinoid component may comprise an active RAR ligand which is substantially ineffective to bind to or activate or block RXRs and/or a precursor of an active RAR ligand substantially ineffective to bind to or activate or block RXRs.

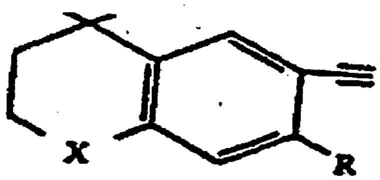
Among the retinoid components useful in the present invention include the following compounds of formula I

Formula I



wherein X is S, O, or NR= where R= is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0-2; and B is H, -COOH or a pharmaceutically acceptable salt, ester or amide thereof, -CH_2OH or an ether or ester derivative, or -CHO or an acetal derivative, or -COR_1 or a ketal derivative where R_1 is -(-CH_2)$_m$$CH_3$ where m is 0-4.

The compounds of formula I can be made by reacting a compound of formula II with a compound of formula III in the presence of cuprous iodide and $Pd(PQ_3)_2Cl_2$ or a similar complex. Compounds of formula II and formula III are as follows:



II

$X'—A—(CH_2)_n—B$

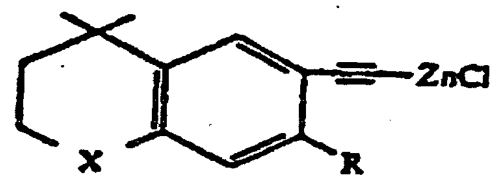
III

Formula II

Formula III

where X= is a halogen, preferably I; n and A are the same as defined above; and B is H, or a protected acid, alcohol, aldehyde or ketone, giving the corresponding compound of formula I.

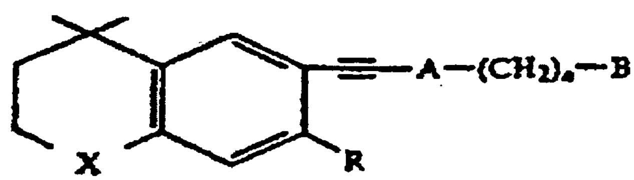
Alternately, the compounds of formula I can be made by reacting a zinc salt of formula IV with a compound of formula III in the presence of $Pd(PQ_3)_4$ (Q is phenyl) or a similar complex,



Formula IV

giving the corresponding compound of formula I.

Further, the compounds of formula I can be made by homologating a compound of formula V



Formula V

where

n is 0-1 to give an acid of formula I; or
converting an acid of formula I to a salt; or
forming an acid addition salt;
converting an acid of formula I to an ester; or
converting an acid of formula I to an amide; or
reducing an acid of formula I to an alcohol or aldehyde; or
converting an alcohol of formula I to an ether or ester; or
oxidizing an alcohol of formula I to an aldehyde; or
converting an aldehyde of formula I to an acetal; or
converting a ketone of formula I to a ketal.

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. Where A is -COOH, this term covers the products derived from treatment of this function with alcohols. Where the ester is derived from compounds where A is $-CH_2OH$, this term covers compounds of the formula $-CH-_2OOCR$ where R is any substituted or unsubstituted aliphatic, aromatic or aliphatic-aromatic group.

Preferred esters are derived from the saturated aliphatic alcohols or acids of about 10 or fewer carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and acids of about 5 to about 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids and alcohols. Here, and where ever else used, lower alkyl means having 1 to about 6 carbon atoms. Also preferred are the phenyl or lower alkylphenyl esters.

Amide has the meaning classically accorded that term in organic chemistry. In this instance, it includes the unsubstituted amides and all aliphatic and aromatic mono- and di-substituted amides. Preferred amides are the mono-and di-substituted amides derived from the saturated aliphatic radicals of about 10 or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals of about 5 to about 10 carbon atoms. Particularly preferred amides are those derived from lower alkyl amines. Also preferred are mono- and di-substituted amides derived from the phenyl or lower alkylphenyl amines. Unsubstituted amides are also preferred.

Acetals and ketals include the radicals of the formula -CK where K is $(-OR)_2$. Here, R is lower alkyl. K may also be $-OR_1O-$ where R_1 is lower alkyl of about 2 to about 5 carbon atoms, straight chain or branched.

Certain retinoid components for use in the present implants include those where the ethynyl group and the B group are attached to the 2 and 5 positions respectively of a pyridine ring (the 6 and 3 positions in the nicotinic acid

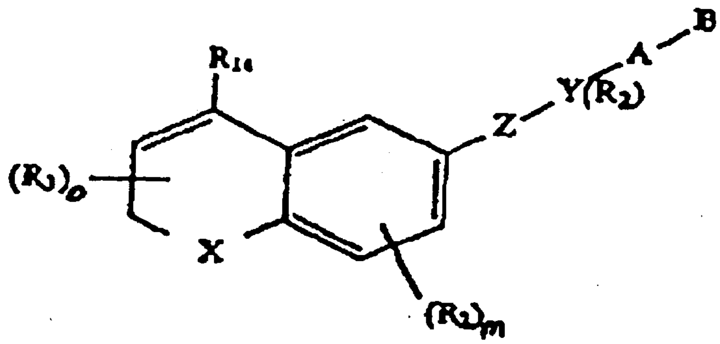
nomenclature being equivalent to the 2/5 designation in the pyridine nomenclature) or the 5 and 2 positions respectively of a thiophene group respectively; n is 0; and B is -COOH, an alkali metal salt or organic amine salt, or a lower alkyl ester, or -CH_2OH and the lower alkyl esters and ethers thereof, or -CHO and acetal derivatives thereof.

More preferred compounds for use in the present systems include:

ethyl 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-nicotinate;
6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid;
6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinic acid;
ethyl 6-(2-(4,4-dimethylchroman-6-yl)ethynyl) nicotinate;
ethyl 6-(2-(4,4,7-trimethylthiochroman-6-yl)ethynyl)-nicotinate;
ethyl 6-(2-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)ethynyl)nicotinate;
ethyl 5-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-thiophene-2-carboxylate;
6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-3-pyridylmethanol; and
2-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-5-pyridinecarboxaldehyde.

These compounds, and methods of making these compounds are described in U.S. Patent 5,089,509.

A class of useful retinoid components has the structure:



STRUCTURE A

wherein X is S, O, NR' where R' is H or alkyl of 1 to 6 carbons, or

X is $[C(R_1)_2]_n$ where R_1 is independently H or alkyl of 1 to 6 carbons, and n is an integer between, and including, 0 and 2, and;

R_2 is hydrogen, lower alkyl of 1 to 6 carbons, F, Cl, Br, I, CF_3, fluoro substituted alkyl of 1 to 6 carbons, OH, SH, alkoxy of 1 to 6 carbons, or alkylthio of 1 to 6 carbons, and;

R_3 is hydrogen, lower alkyl of 1 to 6 carbons or F, and;

m is an integer having the value of 0-3, and;

o is an integer having the value of 0-3, and;

Z is -C≡C-,
-N=N-,
$-N=CR_1-$,
$-CR_1=N$,

$-(CR_1{=}CR_1)_{n'}-$ where n' is an integer having the value 0 - 5,
$-CO-NR_1-$,
$-CS-NR_1-$,
$-NR_1-CO$,
$-NR_1-CS$,
-COO-,
-OCO-;
-CSO-;
-OCS-;

Y is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being optionally substituted with one or two R_2 groups, or

when Z is $-(CR_1{=}CR_1)_{n'}-$ and n' is 3, 4 or 5 then Y represents a direct valence bond between said $(CR_2{=}CR_2)_{n'}$ group and B;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7OR_{13}O$, or tri-lower alkylsilyl, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or trimethylsilylalkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons, and

R_{14} is $(R_{15})_r$-phenyl, $(R_{15})_r$-naphthyl, or $(R_{15})_r$- heteroaryl where the heteroaryl group has 1 to 3 heteroatoms selected from the group consisting of O, S and N, r is an integer having the values of 0 - 5, and

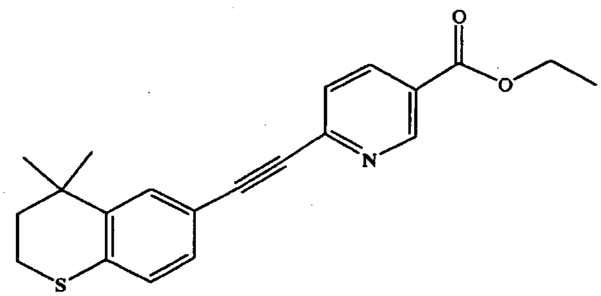
R_{15} is independently H, F, Cl, Br, I, NO_2, $N(R_8)_2$, $N(R_8)COR_8$, $NR_8CON(R_8)_2$, OH, $OCOR_8$, OR_8, CN, an alkyl group having 1 to 10 carbons, fluoro substituted alkyl group having 1 to 10 carbons, an alkenyl group having 1 to 10 carbons and 1 to 3 double bonds, alkynyl group having 1 to 10 carbons and 1 to 3 triple bonds, or a trialkylsilyl or trialkylsilyloxy group where the alkyl groups independently have 1 to 6 carbons.

Such compounds can be made using well known techniques. For example, see U.S. Patent 5,776,699.

One particularly useful class of retinoid components for use in the present invention is selected from active acetylenic retinoid agents, precursors of active acetylenic retinoid agents and mixtures thereof. Active acetylenic retinoid agents includes active retinoid agents including at least one -C̃C- group. Examples of such retinoid components are set forth elsewhere herein.

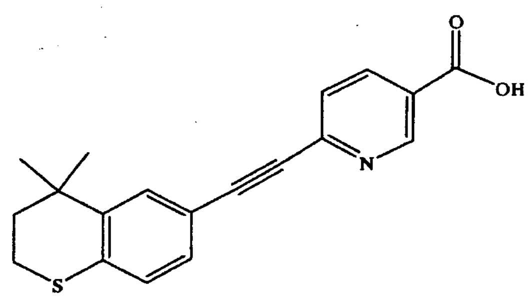
Especially useful retinoid components useful in the present methods include tazarotene, tazarotenic acid and mixtures thereof. Particularly effective results are obtained when tazarotene is employed as the retinoid component.

In one embodiment, an intraocular drug delivery system comprises a compound represented by the following formula:



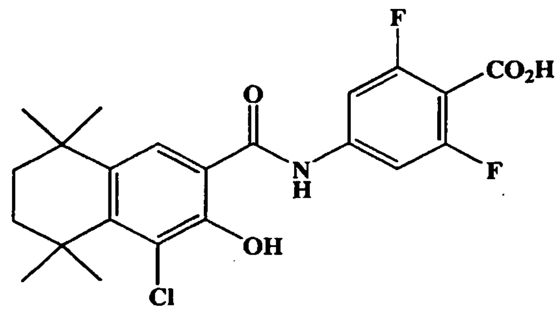
This compound is tazarotene, and for purposes of convenience, it may be referred to as Compound A in this application.

In another embodiment, an intraocular drug delivery system comprises a compound represented by the following formula:



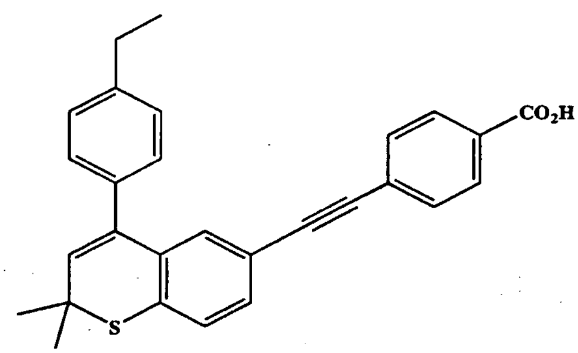
The above compound is tazarotenic acid, and for purposes of convenience, it may be referred to as Compound B in this application.

In another embodiment, an intraocular drug delivery system comprises a compound represented by the following formula:



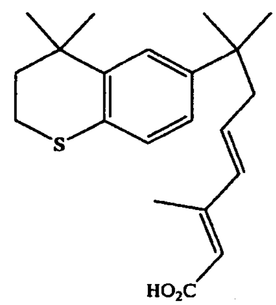
For purposes of convenience, this compound will be referred to as Compound C in this application.

In another embodiment, an intraocular drug delivery system comprises a compound represented by the following formula:



For purposes of convenience, this compound will be referred to as Compound D in this application.

In another embodiment, an intraocular drug delivery system comprises a compound represented by the following formula:



For purposes of convenience, this compound will be referred to as Compound E in this application.

These drug delivery systems may also include salts of the retinoid component. Pharmaceutically acceptable acid addition salts of the compounds of the systems are those formed from acids which form non-toxic addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulfate, or bisulfate, phosphate or acid phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate and p-toluene sulphonate salts.

Thus, the drug delivery system may comprise a therapeutic component which comprises, consists essentially of, or consists of, a retinoid, such as tazarotenic acid, tazarotenic acid precursors, salts thereof, and mixtures thereof. These elements of the therapeutic component may be understood to be a retinoid component. The biodegradable polymer matrix of such systems may be substantially free of polyvinyl alcohol, or in other words, includes no polyvinyl alcohol.

Additional retinoid components may be obtained using conventional methods, such as by routine chemical synthesis methods known to persons of ordinary skill in the art. Some examples of structures and methods of making retinoid components, are provided in U.S. Patent No. 5,776,699, U.S. Patent No. 5,958,954, U.S. Patent No. 5,877,207, and U.S. Patent No. 5,919,970.

Therapeutically effective retinoid components may be screened and identified using conventional screening technologies. In a broad sense, any compound can be tested for RAR activity, for example, using conventional and well known techniques, for example, without limitation, those described in the above-noted patents.

Once a compound has been determined to have suitable RAR activity, it can be administered to a test animal with appropriate monitoring for side effects. Comparing the results of such monitoring with similar monitoring of test animals given reference retinoid agents allows one to determine if the compound is useful in accordance with the present invention.

In other aspects of the present invention, one or more compounds, for example, from a screening library of compounds, which are known to have or have been tested, using conventional and well known techniques, and found to have useful RAR activity, can be individually or collectively tested for RXR activity using conventional and well known testing procedures (see, for example, U.S. Patent 5,906,920).

Compounds with substantially no RXR activity may be selected for further testing. Compounds with desired RAR activity and substantially no RXR activity are useful in accordance with one or more aspects of the present invention.

Other well known and straightforward test methods and/or assays may be employed to determine the selectivity or specificity of an RAR active compound to RAR-alpha, RAR-beta and RAR-gamma. For example, using conventional and well known assays, for example, such as set forth in U.S. Patent 5,776,699, and/or the above-noted patents, the selectively or specificity of a compound to RAR-alpha, RAR-beta and RAR-gamma can be determined. Based on the results of such assays, one can determine whether or not a compound is useful in accordance with one or more aspects of the present invention.

Further confirmation that any compound is useful in accordance with the present invention can be obtained by orally administering the compound to an animal and monitoring the presence or absence of side effects.

In any event, determining which compounds are useful in accordance with the present invention can be accomplished using conventional and well known techniques, without undue experimentation.

The retinoid component may be in a particulate or powder form and entrapped by the biodegradable polymer matrix. Usually, retinoid component particles in intraocular implants will have an effective average size less than about 3000 nanometers. In certain implants, the particles may have an effective average particle size about an order of magnitude smaller than 3000 nanometers. For example, the particles may have an effective average particle size of less than about 500 nanometers. In additional implants, the particles may have an effective average particle size of less than about 400 nanometers, and in still further embodiments, a size less than about 200 nanometers.

The retinoid component of an intraocular drug delivery system is preferably from about 10% to 90% by weight of the system. More preferably, the retinoid component is from about 20% to about 80% by weight of the system. In a preferred embodiment, the retinoid component comprises about 40% by weight of the system (e.g., 30%-50%). In another embodiment, the retinoid component comprises about 60% by weight of the system.

Suitable polymeric materials or compositions for use in the drug delivery systems include those materials which are compatible, that is biocompatible, with the eye so as to cause no substantial interference with the functioning or physiology of the eye. Such materials preferably are at least partially and more preferably substantially completely biodegradable or bioerodible.

Examples of useful polymeric materials include, without limitation, such materials derived from and/or including organic esters and organic ethers, which when degraded result in physiologically acceptable degradation products, including the monomers. Also, polymeric materials derived from and/or including, anhydrides, amides, orthoesters and the like, by themselves or in combination with other monomers, may also find use. The polymeric materials may be addition or condensation polymers, advantageously condensation polymers. The polymeric materials may be cross-linked or non-cross-linked, for example not more than lightly cross-linked, such as less than about 5%, or less than about 1% of the polymeric material being cross-linked. For the most part, besides carbon and hydrogen, the polymers will include at least one of oxygen and nitrogen, advantageously oxygen. The oxygen may be present as oxy, e.g. hydroxy or ether, carbonyl, e.g. non-oxo-carbonyl, such as carboxylic acid ester, and the like. The nitrogen may be present as amide, cyano and amino. The polymers set forth in Heller, Biodegradable Polymers in Controlled Drug Delivery, In: CRC Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 1, CRC Press, Boca Raton, FL 1987, pp 39-90, which describes encapsulation for controlled drug delivery, may find use in the present implants.

Of additional interest are polymers of hydroxyaliphatic carboxylic acids, either homopolymers or copolymers, and polysaccharides. Polyesters of interest include polymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, polycaprolactone, and combinations thereof. Generally, by employing the L-lactate or D-lactate, a slowly eroding polymer or polymeric material is achieved, while erosion is substantially enhanced with the lactate racemate.

Among the useful polysaccharides are, without limitation, calcium alginate, and functionalized celluloses, particularly carboxymethylcellulose esters characterized by being water insoluble, a molecular weight of about 5 kD to 500 kD, for example.

Other polymers of interest include, without limitation, polyesters, polyethers and combinations thereof which are biocompatible and may be biodegradable and/or bioerodible.

Some preferred characteristics of the polymers or polymeric materials for use in the present invention may include biocompatibility, compatibility with the therapeutic component, ease of use of the polymer in making the drug delivery systems of the present invention, a half-life in the physiological environment of at least about 6 hours, preferably greater than about one day, not significantly increasing the viscosity of the vitreous, and water insolubility.

The biodegradable polymeric materials which are included to form the matrix are desirably subject to enzymatic or hydrolytic instability. Water soluble polymers may be cross-linked with hydrolytic or biodegradable unstable cross-links to provide useful water insoluble polymers. The degree of stability can be varied widely, depending upon the choice of monomer, whether a homopolymer or copolymer is employed, employing mixtures of polymers, and whether the polymer includes terminal acid groups.

Equally important to controlling the biodegradation of the polymer and hence the extended release profile of the system is the relative average molecular weight of the polymeric composition employed in the system. Different molecular weights of the same or different polymeric compositions may be included in the system to modulate the release profile. In certain systems, the relative average molecular weight of the polymer will range from about 9 to about 64 kD, usually from about 10 to about 54 kD, and more usually from about 12 to about 45 kD.

In some drug delivery systems, copolymers of glycolic acid and lactic acid are used, where the rate of biodegradation is controlled by the ratio of glycolic acid to lactic acid. The most rapidly degraded copolymer has roughly equal amounts of glycolic acid and lactic acid. Homopolymers, or copolymers having ratios other than

equal, are more resistant to degradation. The ratio of glycolic acid to lactic acid will also affect the brittleness of the drug delivery system, where a more flexible system is desirable for larger geometries. The % of polylactic acid in the polylactic acid polyglycolic acid (PLGA) copolymer can be 0-100%, preferably about 15-85%, more preferably about 35-65%. In some drug delivery systems, a 50/50 PLGA copolymer is used.

The biodegradable polymer matrix of the intraocular drug delivery system may comprise a mixture of two or more biodegradable polymers. For example, the implant may comprise a mixture of a first biodegradable polymer and a different second biodegradable polymer. One or more of the biodegradable polymers may have terminal acid groups.

Release of a drug from an erodible polymer is the consequence of several mechanisms or combinations of mechanisms. Some of these mechanisms include desorption from the systems surface, dissolution, diffusion through porous channels of the hydrated polymer and erosion. Erosion can be bulk or surface or a combination of both. As discussed herein, the matrix of the intraocular drug delivery system may release drug at a rate effective to sustain release of an amount of the retinoid component for more than one week after implantation into an eye. In certain systems, therapeutic amounts of the retinoid component are released for more than about one month, and even for about six months or more.

One example of the biodegradable intraocular drug delivery system comprises tazarotene, tazarotenic acid, or a combination thereof with a biodegradable polymer matrix that comprises a poly (lactide-co-glycolide) or a poly (D,L-lactide-co-glycolide). The system may have an amount of the retinoid component from about 40% to about 70% by weight of the system. Such a mixture is effective in sustaining release of a therapeutically effective amount of the retinoid component for a time period from about one month to about four months from the time the system is placed in an eye.

The release of the retinoid component from the intraocular drug delivery system comprising a biodegradable polymer matrix may include an initial burst of release followed by a gradual increase in the amount of the retinoid component released, or the release may include an initial delay in release of the retinoid component followed by an increase in release. When the drug delivery system is substantially completely degraded, the percent of the retinoid component that has been released is about one hundred. Compared to existing drug delivery systems, the drug delivery systems disclosed herein do not completely release, or release about 100% of the retinoid component, until after about one week of being placed in an eye.

It may be desirable to provide a relatively constant rate of release of the retinoid component from the drug delivery system over the life of the system. For example, it may be desirable for the retinoid component to be released in amounts from about 0.01 μg to about 2 μg per day for the life of the system. However, the release rate may change to either increase or decrease depending on the formulation of the biodegradable polymer matrix. In addition, the release profile of the retinoid component may include one or more linear portions and/or one or more non-linear portions. Preferably, the release rate is greater than zero once the system has begun to degrade or erode.

The drug delivery systems may be monolithic, i.e. having the active agent or agents homogenously distributed through the polymeric matrix, or encapsulated, where a reservoir of active agent is encapsulated by the polymeric matrix. Due to ease of manufacture, monolithic systems are usually preferred over encapsulated forms. However, the greater control afforded by the encapsulated, reservoir-type implants may be of benefit in some circumstances, where the therapeutic level of the drug falls within a narrow window. In addition, the therapeutic component, including the retinoid component, may be distributed in a non-homogenous pattern in the

matrix. For example, an implant may include a portion that has a greater concentration of the retinoid component relative to a second portion of the implant.

The intraocular drug delivery systems disclosed herein may have a size of between about 5 µm and about 2 mm, or between about 10 µm and about 1 mm for administration with a needle, greater than 1 mm, or greater than 2 mm, such as 3 mm or up to 10 mm, for administration by surgical implantation. The vitreous chamber in humans is able to accommodate relatively large implants of varying geometries, having lengths of, for example, 1 to 10 mm. An implant may be a cylindrical pellet (e. g., rod) with dimensions of about 2 mm x 0.75 mm diameter. Or an implant may be a cylindrical pellet with a length of about 7 mm to about 10 mm, and a diameter of about 0.75 mm to about 1.5 mm.

Intraocular implants may also be at least somewhat flexible so as to facilitate both insertion of the implant in the eye, such as in the vitreous, and accommodation of the implant. The total weight of the implant is usually about 250-5000 μg, more preferably about 500-1000 μg. For example, an implant may be about 500 μg, or about 1000 μg. For non-human individuals, the dimensions and total weight of the implant(s) may be larger or smaller, depending on the type of individual. For example, humans have a vitreous volume of approximately 3.8 ml, compared with approximately 30 ml for horses, and approximately 60-100 ml for elephants. An implant sized for use in a human may be scaled up or down accordingly for other animals, for example, about 8 times larger for an implant for a horse, or about, for example, 26 times larger for an implant for an elephant.

Thus, implants can be prepared where the center may be of one material and the surface may have one or more layers of the same or a different composition, where the layers may be cross-linked, or of a different molecular weight, different density or porosity, or the like. For example, where it is desirable to quickly release an initial bolus of drug, the center may be a polylactate coated with a polylactate-polyglycolate copolymer, so as to enhance the rate of initial degradation.

Alternatively, the center may be polyvinyl alcohol coated with polylactate, so that upon degradation of the polylactate exterior the center would dissolve and be rapidly washed out of the eye.

The drug delivery systems may be of any geometry including fibers, sheets, films, microspheres, spheres, circular discs, plaques and the like. The upper limit for the implant size will be determined by factors such as toleration for the implant, size limitations on insertion, ease of handling, etc. Where sheets or films are employed, the sheets or films will be in the range of at least about 0.5 mm x 0.5 mm, usually about 3-10 mm x 5-10 mm with a thickness of about 0.1-1.0 mm for ease of handling. Where fibers are employed, the fiber diameter will generally be in the range of about 0.05 to 3 mm and the fiber length will generally be in the range of about 0.5-10 mm. Spheres may be in the range of about 0.5 μm to 4 mm in diameter, with comparable volumes for other shaped particles.

The size and form of the drug delivery system can also be used to control the rate of release, period of treatment, and drug concentration at the site of implantation. Larger systems will deliver a proportionately larger dose, but depending on the surface to mass ratio, may have a slower release rate. The particular size and geometry of the system are chosen to suit the site of implantation or administration.

The drug delivery systems may be provided in kits, such as sealed packages and the like. The systems may be sterilized or non-sterilized. Advantageously, the present systems remain stable for relatively long periods of time such as six months or more in either sterile or non-sterile settings. For example, the present systems retain their physical appearance and release profiles of the therapeutic component, such as the retinoid component for at least 6 months, and even for at least a year under temperature ranges from about twenty degrees Celsius to about fourty degrees Celsius. Thus, the systems may be stored for substantial periods of time without significant loss of therapeutic efficacy.

The proportions of retinoid component, polymer, and any other modifiers may be empirically determined by formulating several drug delivery systems with varying proportions. A USP approved method for dissolution or release test can be used to measure the rate of release (USP 23; NF 18 (1995) pp. 1790-1798). For example, using the infinite sink method, a weighed sample of the implant is added to a measured volume of a solution containing 0.9% NaCl in water, where the solution volume will be such that the drug concentration is after release is less than 5% of saturation. The mixture is maintained at 37°C and stirred slowly to maintain the implants in suspension. The appearance of the dissolved drug as a function of time may be followed by various methods known in the art, such as spectrophotometrically, HPLC, mass spectroscopy, etc. until the absorbance becomes constant or until greater than 90% of the drug has been released.

In addition to the retinoid component included in the intraocular drug delivery systems disclosed herein, the intraocular systems may also include one or more additional ophthalmically acceptable therapeutic agents. For example, the systems may include one or more antihistamines, one or more antibiotics, one or more beta blockers, one or more steroids, one or more antineoplastic agents, one or more immunosuppressive agents, one or more antiviral agents, one or more antioxidant agents, and mixtures thereof.

Pharmacologic or therapeutic agents which may find use in the present systems, include, without limitation, those disclosed in U.S. Pat. Nos. 4,474,451, columns 4-6 and 4,327,725, columns 7-8.

Examples of antihistamines include, and are not limited to, loradatine, hydroxyzine, diphenhydramine, chlorpheniramine, brompheniramine, cyproheptadine, terfenadine, clemastine, triprolidine, carbinoxamine, diphenylpyraline, phenindamine, azatadine, tripelennamine, dexchlorpheniramine,

dexbrompheniramine, methdilazine, and trimprazine doxylamine, pheniramine, pyrilamine, chiorcyclizine, thonzylamine, and derivatives thereof.

Examples of antibiotics include without limitation, cefazolin, cephradine, cefaclor, cephapirin, ceftizoxime, cefoperazone, cefotetan, cefutoxime, cefotaxime, cefadroxil, ceftazidime, cephalexin, cephalothin,, cefamandole, cefoxitin, cefonicid, ceforanide, ceftriaxone, cefadroxil, cephradine, cefuroxime, cyclosporine, ampicillin, amoxicillin, cyclacillin, ampicillin, penicillin G, penicillin V potassium, piperacillin, oxacillin, bacampicillin, cloxacillin, ticarcillin, azlocillin, carbenicillin, methicillin, nafcillin, erythromycin, tetracycline, doxycycline, minocycline, aztreonam, chloramphenicol, ciprofloxacin hydrochloride, clindamycin, metronidazole, gentamicin, lincomycin, tobramycin, vancomycin, polymyxin B sulfate, colistimethate, colistin, azithromycin, augmentin, sulfamethoxazole, trimethoprim, gatifloxacin, ofloxacin, and derivatives thereof.

Examples of beta blockers include acebutolol, atenolol, labetalol, metoprolol, propranolol, timolol, and derivatives thereof.

Examples of steroids include corticosteroids, such as cortisone, prednisolone, flurometholone, dexamethasone, medrysone, loteprednol, fluazacort, hydrocortisone, prednisone, betamethasone, prednisone, methylprednisolone, riamcinolone hexacatonide, paramethasone acetate, diflorasone, fluocinonide, fluocinolone, triamcinolone, derivatives thereof, and mixtures thereof.

Examples of antineoplastic agents include adriamycin, cyclophosphamide, actinomycin, bleomycin, duanorubicin, doxorubicin, epirubicin, mitomycin, methotrexate, fluorouracil, carboplatin, carmustine (BCNU), methyl-CCNU, cisplatin, etoposide, interferons, camptothecin and derivatives thereof, phenesterine, taxol and derivatives thereof, taxotere and derivatives thereof, vinblastine, vincristine, tamoxifen, etoposide, piposulfan, cyclophosphamide, and flutamide, and derivatives thereof.

Examples of immunosuppresive agents include cyclosporine, azathioprine, tacrolimus, and derivatives thereof.

Examples of antiviral agents include interferon gamma, zidovudine, amantadine hydrochloride, ribavirin, acyclovir, valciclovir, dideoxycytidine, phosphonoformic acid, ganciclovir and derivatives thereof.

Examples of antioxidant agents include ascorbate, alpha-tocopherol, mannitol, reduced glutathione, various carotenoids, cysteine, uric acid, taurine, tyrosine, superoxide dismutase, lutein, zeaxanthin, cryotpxanthin, astazanthin, lycopene, N-acetyl-cysteine, carnosine, gamma-glutamylcysteine, quercitin, lactoferrin, dihydrolipoic acid, citrate, Ginkgo Biloba extract, tea catechins, bilberry extract, vitamins E or esters of vitamin E, retinyl palmitate, and derivatives thereof.

Other therapeutic agents include squalamine, carbonic anhydrase inhibitors, alpha agonists, prostamides, prostaglandins, antiparasitics, antifungals, and derivatives thereof.

The amount of active agent or agents employed in the drug delivery systems, individually or in combination, will vary widely depending on the effective dosage required and the desired rate of release from the system. As indicated herein, the agent will be at least about 1, more usually at least about 10 weight percent of the system, and usually not more than about 80, more usually not more than about 40 weight percent of the system.

In addition to the therapeutic component, the intraocular drug delivery systems disclosed herein may include effective amounts of buffering agents, preservatives and the like. Suitable water soluble buffering agents include, without limitation, alkali and alkaline earth carbonates, phosphates, bicarbonates, citrates, borates, acetates, succinates and the like, such as sodium phosphate, citrate,

borate, acetate, bicarbonate, carbonate and the like. These agents advantageously present in amounts sufficient to maintain a pH of the system of between about 2 to about 9 and more preferably about 4 to about 8. As such the buffering agent may be as much as about 5% by weight of the total drug delivery system. Suitable water soluble preservatives include sodium bisulfite, sodium bisulfate, sodium thiosulfate, ascorbate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, parabens, methylparaben, polyvinyl alcohol, benzyl alcohol, phenylethanol and the like and mixtures thereof. These agents may be present in amounts of from 0.001 to about 5% by weight and preferably 0.01 to about 2% by weight.

In addition, the drug delivery systems may include a solubility enhancing component provided in an amount effective to enhance the solubility of the retinoid component relative to substantially identical systems without the solubility enhancing component. For example, an implant may include a β-cyclodextrin, which is effective in enhancing the solubility of the retinoid component. The β-cyclodextrin may be provided in an amount from about 0.5% (w/w) to about 25% (w/w) of the implant. In certain implants, the β-cyclodextrin is provided in an amount from about 5% (w/w) to about 15% (w/w) of the implant.

In some situations mixtures of drug delivery systems may be utilized employing the same or different pharmacological agents. In this way, a cocktail of release profiles, giving a biphasic or triphasic release with a single administration is achieved, where the pattern of release may be greatly varied.

Additionally, release modulators such as those described in U. S. Patent No. 5,869,079 may be included in the implants. The amount of release modulator employed will be dependent on the desired release profile, the activity of the modulator, and on the release profile of the retiniod in the absence of modulator. Electrolytes such as sodium chloride and potassium chloride may also be included in the implant. Where the buffering agent or enhancer is hydrophilic, it may also act as

a release accelerator. Hydrophilic additives act to increase the release rates through faster dissolution of the material surrounding the drug particles, which increases the surface area of the drug exposed, thereby increasing the rate of drug bioerosion. Similarly, a hydrophobic buffering agent or enhancer dissolve more slowly, slowing the exposure of drug particles, and thereby slowing the rate of drug bioerosion.

Various techniques may be employed to produce the drug delivery systems described herein. Useful techniques include, but are not necessarily limited to, solvent evaporation methods, phase separation methods, interfacial methods, molding methods, injection molding methods, extrusion methods, co-extrusion methods, carver press method, die cutting methods, heat compression, combinations thereof and the like.

Specific methods are discussed in U.S. Pat. No. 4,997,652. Extrusion methods may be used to avoid the need for solvents in manufacturing. When using extrusion methods, the polymer and drug are chosen so as to be stable at the temperatures required for manufacturing, usually at least about 85 degrees Celsius. Extrusion methods use temperatures of about 25 degrees C to about 150 degrees C, more preferably about 65 degrees C to about 130 degrees C. An implant may be produced by bringing the temperature to about 60 degrees C to about 150 degrees C for drug/polymer mixing, such as about 130 degrees C, for a time period of about 0 to 1 hour, 0 to 30 minutes, or 5-15 minutes. For example, a time period may be about 10 minutes, preferably about 0 to 5 min. The implants are then extruded at a temperature of about 60 degrees C to about 130 degrees C, such as about 75 degrees C. Preferably, the temperature is not substantially greater than the denaturation temperature associated with the therapeutic agent.

In addition, the implant may be coextruded so that a coating is formed over a core region during the manufacture of the implant.

Compression methods may be used to make the implants, and typically yield implants with faster release rates than extrusion methods. Compression methods may use pressures of about 50-150 psi, more preferably about 70-80 psi, even more preferably about 76 psi, and use temperatures of about 0 degrees C to about 115 degrees C, more preferably about 25 degrees C.

In addition, the implants, particularly implants which are cut to the desired size and shape, such as wafer implants, may include an additive, such as a lubricant, that is effective to reduce the brittleness of the implant relative to substantially identical implants that do not have an additive. By providing such an additive in the implant, the amount of damaged or unusable implants due to breakage is substantially reduced.

Microparticles may be produced using a solvent evaporation process. Such a process may include steps of liquid sieving, freeze drying, and sterilizing the various composition components. In one embodiment, a retinoid component and a polymeric component can be combined with methylene chloride to form a first composition, and water and polyvinyl alcohol can be combined to form a second composition. The first and second compositions can be combined to form an emulsion. The emulsion can be rinsed and/or centrifuged, and the resulting product can be dried. In a further embodiment, the emulsion undergoes an evaporation process to remove methylene chloride from the emulsion. For example, the emulsion can be evaporated for about 2 days or more. In this embodiment, the method comprises sieving retinoid-containing microspheres in a liquid phase, as compared to a method which comprises sieving retinoid-containing microparticles in a dry phase. This method can also comprise a step of freeze drying the sieved microparticles, and a step of packaging the freeze dried microparticles. Another example of a method for producing retinoid-containing microspheres is disclosed in U.S. Patent Publication No. 2005/0003007 (Boix et al.).

Thus, in one embodiment, a method of producing retinoid-containing microspheres can comprise one or more of the following steps. In certain embodiments, the method comprises each of the following steps. A polymeric material, such as PLGA, is dissolved in a solvent, such as methylene chloride. The dissolving of the PLGA can occur with stirring the mixture until the PLGA is completely dissolved. A predetermined amount of a retinoid component, such as tazarotene, is added to the dissolved PLGA composition. The resulting composition can be understood to be a first composition in reference to this method. A second different composition is produced by combining heated water, for example water having a temperature of about 80 degrees C, with polyvinylic alcohol (PVA). The PVA can be combined with the heated water by stirring the water at a rate effective in maintaining PVA in suspension without substantial bubble formation. The second composition may then be cooled to a desired temperature, such as room temperature.

An emulsion can be produced by combining the first composition and the second composition described in the preceding paragraph. For example, the second composition (i.e., the PVA solution) can be vigorously stirred while avoiding bubble formation. While stirring the second composition, the first composition is added to form an emulsion. As the mixture emulsifies, the stirring speed may be increased to keep the surface of the emulsion moving. Foam or bubble formation is minimized during these steps. In this method, the emulsion is stirred for at least two days (e.g., for about 48 hours or more). As the emulsion is stirred for about 24 hours, the emulsion begins to liquefy. To reduce the possibility of foaming, the stirring speed can be decreased as the emulsion liquefies. After about 48 hours, methylene chloride is substantially or completely evaporated. The method can include a step of determining the amount of methylene chloride in the evaporated material.

After the evaporation of the methylene chloride, the microparticle-containing composition is rinsed and sieved. For example, the microparticle-containing

composition is combined with a liquid and centrifuged. The supernatant is removed and the pellet can be resuspended by sonication or other suitable method for additional centrifugation steps. After the microsphere suspension has been centrifuged, water can be added to rinse the microspheres, and the resulting supernatant can be removed by vacuum extraction. In preferred methods, at least three water rinsing steps are desirable. The rinsed pellets are then sieved through a plurality of filters. For example, the pellets can be passed through two superimposed filters having a pore size of about 125 micrometers and about 45 micrometers, respectively. The filters can be rinsed with water and the solution can be retrieved in the filter bottom.

The retrieved solution can then be combined with an additional amount of water and rinsed two or more times using a centrifuge. The rinsed pellet can then be placed in the filter bottom and covered with a filter to reduce loss of the microsphere material during a lyophilization procees. The material is then frozen. For example, the material is frozen at fifty degrees C and freeze dried for at least twelve hours. After freeze drying, the microspheres can be stored in a package, and/or may be sterilized by a sterilization device, such as a source of gamma radiation.

The drug delivery systems of the present invention may be inserted into the eye, for example the vitreous chamber of the eye, by a variety of methods, including placement by forceps or by trocar following making a 2-3 mm incision in the sclera. One example of a device that may be used to insert the implants into an eye is disclosed in U.S. Patent Publication No. 2004/0054374. The method of placement may influence the therapeutic component or drug release kinetics. For example, delivering an implant with a trocar may result in placement of the implant deeper within the vitreous than placement by forceps, which may result in the implant being closer to the edge of the vitreous. The location of the implant may influence the concentration gradients of therapeutic component or drug surrounding the element, and thus influence the release rates *(e.g.,* an element placed closer to the edge of

the vitreous may result in a slower release rate). Microspheres of the present invention can be injected into the vitreous of an eye using a needle or similar device.

The present drug delivery systems are configured to release an amount of the retinoid component effective to treat or reduce a symptom of an ocular condition, such as an ocular condition related to proliferative vitreal retinopathy, age related macular degeneration, diabetic retinopathy and retinitis pigementosa, among others.

The present systems disclosed herein may also be configured to release the retiniod or additional therapeutic agents, as described above, which to prevent diseases or conditions, such as the following:

MACULOPATHIES/RETINAL DEGENERATION: Non-Exudative Age Related Macular Degeneration (ARMD), Exudative Age Related Macular Degeneration (ARMD), Choroidal Neovascularization, Diabetic Retinopathy, Acute Macular Neuroretinopathy, Central Serous Chorioretinopathy, Cystoid Macular Edema, Diabetic Macular Edema.

UVEITIS/RETINITIS/CHOROIDITIS: Acute Multifocal Placoid Pigment Epitheliopathy, Behcet's Disease, Birdshot Retinochoroidopathy, Infectious (Syphilis, Lyme, Tuberculosis, Toxoplasmosis), Intermediate Uveitis (Pars Planitis), Multifocal Choroiditis, Multiple Evanescent White Dot Syndrome (MEWDS), Ocular Sarcoidosis, Posterior Scleritis, Serpignous Choroiditis, Subretinal Fibrosis and Uveitis Syndrome, Vogt-Koyanagi-Harada Syndrome.

VASUCLAR DISEASES/ EXUDATIVE DISEASES Retinal Arterial Occlusive Disease, Central Retinal Vein Occlusion, Disseminated Intravascular Coagulopathy, Branch Retinal Vein Occlusion, Hypertensive Fundus Changes, Ocular Ischemic Syndrome, Retinal Arterial Microaneurysms, Coat's Disease, Parafoveal Telangiectasis, Hemi-Retinal Vein Occlusion, Papillophlebitis, Central Retinal Artery Occlusion, Branch Retinal Artery Occlusion, Carotid Artery Disease (CAD), Frosted

Branch Angiitis, Sickle Cell Retinopathy and other Hemoglobinopathies, Angioid Streaks, Familial Exudative Vitreoretinopathy, Eales Disease.

TRAUMATIC/SURGICAL: Sympathetic Ophthalmia, Uveitic Retinal Disease, Retinal Detachment, Trauma, Laser, PDT, Photocoagulation, Hypoperfusion During Surgery, Radiation Retinopathy, Bone Marrow Transplant Retinopathy.

PROLIFERATIVE DISORDERS: Proliferative Vitreal Retinopathy and Epiretinal Membranes, Proliferative Diabetic Retinopathy, Retinopathy of Prematurity (retrolental fibroplastic).

INFECTIOUS DISORDERS: Ocular Histoplasmosis, Ocular Toxocariasis, Presumed Ocular Histoplasmosis Syndrome (POHS), Endophthalmitis, Toxoplasmosis, Retinal Diseases Associated with HIV Infection, Choroidal Disease Associated with HIV Infection, Uveitic Disease Associated with HIV Infection, Viral Retinitis, Acute Retinal Necrosis, Progressive Outer Retinal Necrosis, Fungal Retinal Diseases, Ocular Syphilis, Ocular Tuberculosis, Diffuse Unilateral Subacute Neuroretinitis, Myiasis.

GENETIC DISORDERS: Retinitis Pigmentosa, Systemic Disorders with Accosiated Retinal Dystrophies, Congenital Stationary Night Blindness, Cone Dystrophies, Fundus Flavimaculatus, Best's Disease, Pattern Dystrophy of the Retinal Pigmented Epithelium, X-Linked Retinoschisis, Sorsby's Fundus Dystrophy, Benign Concentric Maculopathy, Bietti's Crystalline Dystrophy, pseudoxanthoma elasticum, Osler Weber syndrome.

RETINAL TEARS/HOLES: Retinal Detachment, Macular Hole, Giant Retinal Tear.

TUMORS: Retinal Disease Associated with Tumors, Solid Tumors, Tumor Metastasis, Benign Tumors, for example, hemangiomas, neurofibromas, trachomas,

and pyogenic granulomas, Congenital Hypertrophy of the RPE, Posterior Uveal Melanoma, Choroidal Hemangioma, Choroidal Osteoma, Choroidal Metastasis, Combined Hamartoma of the Retina and Retinal Pigmented Epithelium, Retinoblastoma, Vasoproliferative Tumors of the Ocular Fundus, Retinal Astrocytoma, Intraocular Lymphoid Tumors.

MISCELLANEOUS: Punctate Inner Choroidopathy, Acute Posterior Multifocal Placoid Pigment Epitheliopathy, Myopic Retinal Degeneration, Acute Retinal Pigment Epithelitis, Ocular inflammatory and immune disorders, ocular vascular malfunctions, Corneal Graft Rejection, Neovascular Glaucoma and the like.

In one embodiment, a drug delivery systems, such as the implants disclosed herein, is administered to a posterior segment of an eye of a human or animal patient, and preferably, a living human or animal. In at least one embodiment, an implant is administered without accessing the subretinal space of the eye. For example, a method of treating a patient may include placing the implant or microparticles directly into the posterior segment of the eye. In other embodiments, a method of treating a patient may comprise administering an implant or microparticles to the patient by at least one of intravitreal injection, subconjuctival injection, sub-tenon injections, retrobulbar injection, and suprachoroidal injection.

In at least one embodiment, a method of improving or maintaining vision in a patient comprises administering one or more implants or microparticles containing one or more retinoid components, as disclosed herein to a patient by at least one of intravitreal injection, subconjuctival injection, sub-tenon injection, retrobulbar injection, and suprachoroidal injection. A syringe apparatus including an appropriately sized needle, for example, a 22 gauge needle, a 27 gauge needle or a 30 gauge needle, can be effectively used to inject the drug delivery system into the posterior segment of an eye of a human or animal. Repeat injections are often not necessary due to the extended release of the retinoid component from the systems.

In another aspect of the invention, kits for treating an ocular condition of the eye are provided, comprising: a) a container or package comprising an extended release implant or microparticles comprising a therapeutic component including a retinoid component, such as a RAR agonist (e.g., tazarotene, tazarotenic acid, or mixtures thereof), and a drug release sustaining component; and b) instructions for use. Instructions may include steps of how to handle the drug delivery systems, how to insert the systems into an ocular region, and what to expect from using the systems.

Example 1

Manufacture and testing of implants containing an retinoid component and a biodegradable polymer matrix

Biodegradable implants are made by combining a retinoid component, such as tazarotene, or tazarotenic acid, with a biodegradable polymer composition in a stainless steel mortar. Other retinoid components may include any one or more of the compounds described hereinabove. The combination is mixed via a Turbula shaker set at 96 RPM for 15 minutes. The powder blend is scraped off the wall of the mortar and then remixed for an additional 15 minutes. The mixed powder blend is heated to a semi-molten state at specified temperature for a total of 30 minutes, forming a polymer/drug melt.

Rods are manufactured by pelletizing the polymer/drug melt using a 9 gauge polytetrafluoroethylene (PTFE) tubing, loading the pellet into the barrel and extruding the material at the specified core extrusion temperature into filaments. The filaments are then cut into about 1 mg size implants or drug delivery systems. The rods have dimensions of about 2 mm long x 0.72 mm diameter. The rod implants weigh between about 900 μg and 1100 μg.

Wafers are formed by flattening the polymer melt with a Carver press at a specified temperature and cutting the flattened material into wafers, each weighing

about 1 mg. The wafers have a diameter of about 2.5 mm and a thickness of about 0.13 mm. The wafer implants weigh between about 900 μg and 1100 μg.

In-vitro release testing can be performed on each lot of implant (rod or wafer). Each implant may be placed into a 24 mL screw cap vial with 10 mL of Phosphate Buffered Saline solution at 37°C and 1 mL aliquots are removed and replaced with equal volume of fresh medium on day 1, 4, 7, 14, 28, and every two weeks thereafter.

Drug assays may be performed by HPLC, which consists of a Waters 2690 Separation Module (or 2696), and a Waters 2996 Photodiode Array Detector. An Ultrasphere, C-18 (2), 5 μm; 4.6 x 150 mm column heated at 30 ° C can be used for separation and the detector can be set at 264 nm. The mobile phase can be (10:90) MeOH - buffered mobile phase with a flow rate of 1 mL/min and a total run time of 12 min per sample. The buffered mobile phase may comprise (68:0.75:0.25:31) 13 mM 1-Heptane Sulfonic Acid, sodium salt - glacial acetic acid – triethylamine - Methanol. The release rates can be determined by calculating the amount of drug being released in a given volume of medium over time in μg/day.

The polymers chosen for the implants can be obtained from Boehringer Ingelheim or Purac America, for example. Examples of polymers include: RG502, RG752, R202H, R203 and R206, and Purac PDLG (50/50). RG502 is (50:50) poly(D,L-lactide-co-glycolide), RG752 is (75:25) poly(D,L-lactide-co-glycolide), R202H is 100% poly(D, L-lactide) with acid end group or terminal acid groups, R203 and R206 are both 100% poly(D, L-lactide). Purac PDLG (50/50) is (50:50) poly(D,L-lactide-co-glycolide). The inherent viscosity of RG502, RG752, R202H, R203, R206 , and Purac PDLG are 0.2, 0.2, 0.2, 0.3, 1.0, and 0.2 dL/g, respectively. The average molecular weight of RG502, RG752, R202H, R203, R206, and Purac PDLG are, 11700, 11200, 6500, 14000, 63300, and 9700 daltons, respectively.

Microspheres can be manufactured with a tazarotene loading of 10% w/w in a biodegradable polymer composition of PLGA. The microspheres can then be sterilized by gamma irradiation at a dose of 2.5 to 4.0 mRad. One formula for a five-gram batch size is provided below:

Component	Use	Quantity
Phase I		
Polyvinyl Alcohol (PVA)	Stabilizer	47.5 grams
Purified Water	Solvent	1600 mL
Phase II		
Tazarotene	Active	Placebo or 1.0 grams
Poly lactide-co-glycolide 75:25 i.v. 0.43 or 0.65	Polymer/ Vehicle	4.50 grams
Methylene Chloride	Solvent	300 mL

In a five-liter beaker, a solution of 3.0 % PVA is manufactured using a high shear impeller and a stirring rate of 400 to 500 rpm at 80 °C. Once in solution the stirring rate is reduced to 200 RPM to minimize foaming. PLGA is then dissolved in the methylene chloride. Once the PLGA is in solution, tazarotene is added and brought into solution.

Microspheres are then manufactured using a solvent evaporation technique. The PVA solution is vigorously stirred while slowly adding the tazarotene/ PLGA solution. The emulsion is then allowed to stir over 48 hours to remove the methylene chloride. The microspheres are then rinsed, dried in vacuum and finally freeze dried. The microspheres are frozen at –50°C, then freeze dried for at least 12 hours at a 4 mbar minimum pressure (400 Pa).

Example 2

Controlled Release of Retinoic Acid Receptor Agonists as a Method of Preventing Proliferation of Retinal Pigmented Epithelium

An intraocular implant comprising an RAR agonist may be prepared as described in Example 1. The implant may include other actives or excipients as needed. The RAR agonist may be released from the implant by diffusion, erosion, dissolution or osmosis. Drug is released from the implant over a period of 7 days to over a period greater than one year. The polymeric implant may be comprised of bioerodible or non-erodible polymers. Bioerodible polymers may include a polyester, poly (ortho ester), poly(phosphazine), poly (phosphate ester), natural polymer such as gelatin or collagen, or a polymeric blend. The platform may be a solid implant, semisolid or viscoelastic. Administration of the drug delivery platform can be accomplished via intravitreal, subconjunctival, subretinal, retro-bulbar implantation or injection. This invention describes the controlled or sustained delivery of retinoic acid receptor (RAR) agonists for the treatment of retinal diseases associated with the proliferation of the retinal pigment epithelium.

Figure 1A and figure 1B illustrate the cumulative percent in-vitro release of tazarotene from PLA and PLGA microsphere implants.

Figure 2 illustrates the cumulative percent in vitro release of tazarotenic acid from polylactide (PLA) and poly(lactide-co-glycolide) (PLGA) implants.

Thus, direct or local administration of the present implants into an ocular region circumvents the side effects and toxicity of systemic administration while reducing the need for multiple intravitreal bolus injections. Controlled or sustained delivery of the retinoid from the implant provides for one time dosing of the retinoid at the time of surgery.

Example 3

Method of Sterilization of PLGA and PLA Microspheres and Bioerodible Implants

Tazarotene-containing microspheres (75:25 PLGA) were prepared as described in Example 1. PLA and PLGA microspheres or implants were gamma irradiated at a dose ranging from 1.0 to 4.5 mRad, such as 2.5 to 4.0 mRad, at low temperatures, such as at 0 °C. The temperature was lowered by the addition of cold packs to the sterilization carton or by lowering the temperature of the environment. Gamma irradiation results in significant aggregation of the microspheres when the temperature is not maintained at or below about five degrees C.

There is a significant aggregation observed as a result of gamma irradiation in both drug loaded and placebo microspheres when the temperature is not maintained at or below about five degrees C. When the microspheres were sterilized at a reduced temperature the aggregation was prevented. Microspheres sterilized at ambient temperatures show a marked aggregation. This includes low molecular weight and high molecular weight PLGA implants loaded with 10% tazarotene. A strong shift towards increase in volume average particle size is observed for all sublots. Those sublots sterilized at reduced temperatures show an almost superimposeable volume and number average particle size distribution with their non-sterilized counterparts.

Thus, PLA and PLGA microspheres have been terminally sterilized thereby reducing the need for aseptic processing, heat or steam sterilization or the use of ethylene oxide. The stability of the PLA and PLGA microspheres and implants sterilized by this method is improved relative to other methods. This is important as the PLA and PLGA polymers are heat and moisture labile. Additionally, the rate of drug release from monolithic implants is the integrated result of diffusional and degradation processes. As such surface area changes encountered with

aggregation will cause significant variability in drug release and implant degradation profile.

Example 4

Sterile Bioerodible Retinal Plug for Intraocular Drug Delivery

The bioerodible plug comprises of one or more bioerodible polymers, a retinoid and other active compounds or excipients. The retinoid is present as the active for the treatment of proliferative vitreal retinopathy (PVR) and retinal neovascularization or to improve the biocompatibility of the device. The bioerodible polymers may include a polyester, poly (ortho ester), poly(phosphazine), poly (phosphate ester), natural polymer such as gelatin or collagen, or a polymeric blend.

The components of the device are extruded as a homogeneous device in the shape of a plug. The plug is then inserted into the vitreous cavity through the sclera, choroid and retina. The distal end of the plug protrudes into the vitreous cavity. A hole drilled into the proximal end of the device is used to suture the plug to the sclera. The plug may be loaded with 0.1 to 40% w/w of pharmacologically active compounds. Drug is released from the plug into the sclera, choroid, retina and vitreous cavity over a period of 7 days to over a period greater than one year.

Incorporation of retinoids (tazarotenic acid, tazarotene, or other retinoid receptor agonist) into the plug can improve the biocompatibility of the implant and provide a therapeutic effec in the prevention or treatment of PVR. The plug may be optimized to resist scleral and choroidal erosion of the plug. This would prevent disinsertion or fragmentation into the vitreous cavity. This may be accomplished by altering the surface finish of the plug, coating the plug with another biodegradable semipermeable polymer, or the addition of another polymer to the blend. Advantageously, organic solvents are not needed for the incorporation of the active agent and excipients into the polymeric matrix. The active compounds, polymers and excipients are milled prior to extrusion. The plug is a homogeneous system that provides for ease of manufacturing and scale-up by simple extrusion technologies.

Further, the polymeric plug may also be manufactured by injection molding. The mechanism and rate of drug release may be controlled by choice of polymer, polymer molecular weight, polymer crystallinity, copolymer ratios, processing conditions, surface finish, geometry, excipient addition and polymeric coatings. Drug may be released from the device by diffusion, erosion, dissolution or osmosis.

The release of the retinoid from the plug may include an initial burst of 10% of the retinoid, and an additional 10% over the first month after placement in an eye.

Some related information may be found in U.S. Pat. Nos. 4,712,500; 5,466,233, and in Kimura, Hideya et. al. A New Vitreal Drug Delivery System using an Implantable Biodegradable Polymeric Device, Invest Ophthalmol Vis Sci . 1994;35 : 2815- 2819; and Hashizoe, Mototane et. al. Scleral Plug of BiodegadablePolymers for Controlled Drug Release in the Vitreous, Arch Ophthalmol . 1994;112 : 1380-1384.

Example 5

Subconjunctival and periocular vitreous drug delivery of prodrugs with improved safety

This example teaches that subconjunctival and periocular administration of ester prodrugs provides a higher therapeutic index than direct intraocular administration of the prodrugs.

The vitreous has a limited capacity to hydrolyze ester prodrugs into their active parent. Although it is counterintuitive, subconjunctival or periocular administration of ester prodrugs is more efficient than direct intraocular administration. This is contrary to what would be anticipated from the current literature. The blood-retinal barriers provide a significant constraint to vitreoretinal drug delivery, as discussed hrein. Circumventing these barriers by direct intraocular administration is the current practice and thought to be the most efficient mode of

delivery. Few compounds are delivered by subconjunctival or periocular administration as this is much less efficient than direct intraocular administration.

In this example it is demonstrated that ester prodrugs can actually be delivered to the vitreous by subconjunctival administration more efficiently than by direct intraocular administration. This is believed to be a result of the differential esterase activity in the choroid and iris-ciliary body versus the vitreous. Interestingly, the ubiquitous nature of esterases in the iris-ciliary body and the choroidal circulation allow for a more efficient vitreous delivery of drug from periocular administration than intraocular injection.

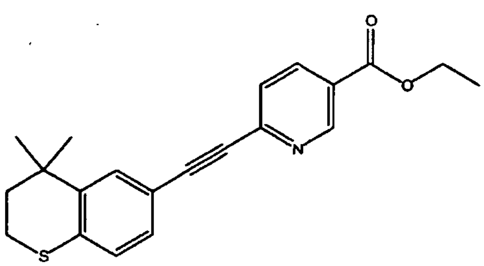
This example demonstrates improvements in pharmacotherapy of compounds with low therapeutic indexes directed at the posterior ocular structures. Thus, this example demonstrates the (i) use of subconjunctival or periocular administration of ester prodrugs for vitreal drug delivery; (ii) use of subconjunctival or periocular administration of ester prodrugs for retinal drug delivery; (iii) subconjunctival or periocular delivery of retinoid ester prodrugs; (iv) subconjunctival or periocular delivery of ester prodrugs of carboxylic acids; (v) subconjunctival or periocular delivery of ester prodrugs of alcohols; (vi) use of subconjunctival or periocular administration of ester prodrugs for the delivery of compounds to the posterior structures of the eye including: uveal tract, vitreous, retina, choroid and retinal pigmented epithelium; (vii) use of subconjunctival or periocular administration of non-ester prodrugs where the enzymes responsible for bioreversion are at a higher activity in the subconjunctival or periocular space than the vitreous. These are for the delivery of compounds to the posterior structures of the eye including: uveal tract, vitreous, retina, choroid and retinal pigmented epithelium.

Thus, implants and methods are provided that will allow for a more efficient vitreoretinal delivery of drugs and thereby allow for improvments in their therapeutic index.

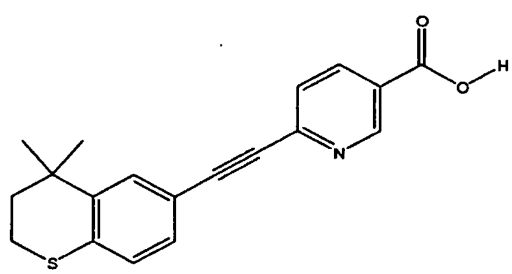
This example utilizes the unique esterase distribution within the eye to deliver drugs to the back of the eye in a more efficient manner. The subconjunctival or periocular space can serve as a depot for an ester prodrug. Facile hydrolysis upon intraocular penetration is more efficient than intravitreal hydrolysis due to the ubiquitous nature of esterases in the iris-ciliary process and the choroidal circulation. The result is: (i) the ability to utilize lipohpilic prodrugs that can enhance trans-retinal penetration while; (ii) lowering intraocular concentrations of the parent prodrug relative to the parent prodrug concentrations achieved after intraocular injection. This is due to more efficient hydrolysis to the active drug; (iii) an improved intraocular prodrug/ drug ratio; and (iv) the creation of a lipophilic depot of compound in the subconjunctival or periocular space for sustained delivery.

Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate (tazarotene) is the ethyl ester of the active retinoid 4,4-dimethyl-6-[2'-(5"-carboxy-2"-pyridyl)-ethynyl]-thiochroman (tazarotenic acid).

Tazarotene



Tazarotenic Acid



Tazarotene is a lipophilic prodrug of tazrotenic acid with a logP of 4.3 and a solubility of 1 μg/ mL in water. Retinoids are known to be therapeutic in treating several conditions of the retina and retinal pigmented epithelium such as retinitis pigmentosa and proliferative vitreal retinopathy. Unfortunately, retinoids are also known to cause cataracts. This is most likely due to the effect of the retinoid on the lens epithelium. Highly lipophilic retinoids have the additional disadvantage of favorable partitioning into the lipophilic lens epithelium. Minimizing the amount of

tazarotene in the vitreous relative to tazarotenic acid may improve the compound's therapeutic index.

General disposition of intraocular and subconjunctivally administered tazarotene and tazarotenic acid was assessed. Briefly, albino rabbits were dosed via intraocular injection with 1.25 μg of tazarotene or tazarotenic acid. Injection was made mid-vitreous. After dosing the vitreous, retina and aqueous humor concentrations of tazarotene and tazarotenic acid were determined at 0.5, 1, 2, 4, 8, 12 and 24 hours post dosing. The data demonstrate that tazarotenic acid is generated from tazarotene in the vitreous. Additionally, the tazarotenic acid concentrations asymptotically approach approximately 10 ng/mL. It appears that the vitreous esterase activity is overwhelmed with the maximal vitreous concentration of tazarotenic acid obtainable after direct intraocular implantation equal to 10 ng/mL. Tazarotenic acid is eliminated in an apparent first order process from the vitreous with a half-life of 4.24 hours after midvitreous dosing of 1.25 μg of tazarotenic acid.

Tazarotene was also dosed in the subconjunctival space. Three dosage forms were evaluated: A tazarotene aqueous suspension (1 mg), a tazarotene subconjunctival olive oil solution (1 mg), and an tazarotene poly (lactide-co-glycolide) microsphere suspension. After dosing, the vitreous, retina and aqueous humor concentrations of tazarotene and tazarotenic acid were determined at 2, 8, 24, 48, 96, 168 and 336 hours post dosing. It was observed that subconjunctival administration achieved significant levels of tazarotene and tazarotenic acid in the ocular tissues. More importantly, the ratio of tazarotene to tazarotenic acid was significantly lower, indicating a higher capacity to hydrolyze the ester prodrug into its parent by this route. The vitreous concentration data is summarized in Table 1. The vitreous concentration time profiles are summarized in Figures 3 through 9.

The data shows a more efficient delivery of tazarotenic acid from subconjunctival delivery compared with intravitreal delivery. The tazarotene/ tazarotenic acid ratio is significantly lower from subconjunctival delivery as shown in

Figure 10. This surprising result is believed to be due to the higher esterase activity of the choroid and iris-ciliary body when compared to the retina. It is also important to note that concentrations of the retinoids tazarotene and tazarotenic acid were maintained at low effective levels for a period of 336 hours.

Thus, the present example describes the (i) use of subconjunctival or periocular administration of ester prodrugs for vitreal drug delivery; (ii) use of subconjunctival or periocular administration of ester prodrugs for retinal drug delivery; (iii) subconjunctival or periocular delivery of retinoid ester prodrugs; (iv) subconjunctival or periocular delivery of ester prodrugs of carboxylic acids; (v) subconjunctival or periocular delivery of ester prodrugs of alcohols; (vi) use of subconjunctival or periocular administration of ester prodrugs for the delivery of compounds to the posterior structures of the eye including: Uveal tract, vitreous, retina, choroid and retinal pigmented epithelium; (vii) use of subconjunctival or periocular administration of non-ester prodrugs where the enzymes responsible for bioreversion are at a higher activity in the subconjunctival or periocular space than the vitreous. These are for the delivery of compounds to the posterior structures of the eye including: Uveal tract, vitreous, retina, choroid and retinal pigmented epithelium.

Table 1. Vitreous Concentrations of tazarotene and tazarotenic acid after Intravitreal and Subconjunctival Dosing.

Dosage Form	Mean Vitreous Concentration tazarotene	Mean Vitreous Concentration tazarotenic acid	tazarotene/ tazarotenic acid ratio
Intravitreal Injection (1.25 μg)	417.0	9.9	42.0
Subconjunctival Suspension (1 mg)	42.0	2.5	16.8
Subconjunctival Microspheres (1 mg)	21.9	1.4	16.1
Subconjunctival Oil Solution (1 mg)	96.2	5.43	17.7

Example 6

Hydrophilic retinoids with reduced Ocular side effects

This example describes hydrophilic retinoids with good oral and topical bioavailability with improved ocular side effect profiles. This example describes the use of retinoids with log partition coefficients (log P) less than 3.0 that have reduced ocular side effects.

TAZAROTENIC ACID OCULAR CONCENTRATIONS

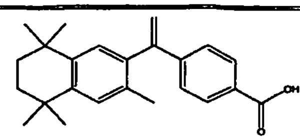
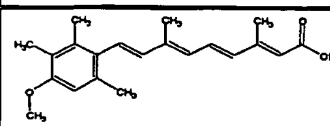
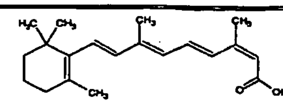
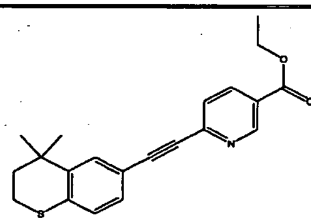
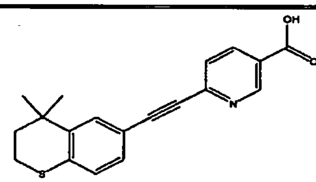
Table 2. Tazarotene and Tazarotenic Acid plasma concentrations after topical and systemic delivery.

Route	Dose (Conc.)	TAZAROTENE Cmax (ng/ mL)	TAZAROTENIC ACID Cmax (ng/ mL)
Topical Gel	0.1% 2% BSA 0.1% 7% BSA 0.1% 15% BSA 0.1% 20% BSA 0.1% Phase 3	Tazarotene concentrations BLQ for > 90%	0.241 0.83 4.80 12.0 90% < 1 ng/ mL
Oral	1.1 mg/ Day	95% < 0.1 ng/ mL	28.9
Oral	3.0 mg/ Day	< 0.1 ng/ mL	81.6
Oral	6.0 mg/ Day	< 0.1 ng/ mL	C_{max} 227 C_{trough} 2.56

Table 2. summarizes the vitreous retinoid levels after topical and oral dosing of tazarotene. For the most part tazarotene is not observed in the plasma after topical or oral administration. Facile hydrolysis by pre-systemic metabolism rapidly generates the free acid. Tazarotenic acid plasma concentrations (Cmax, maximal plasma level) from topical administration range from 0.25 ng/ mL to 12 ng/ mL. It is important to note that these are plasma concentrations and the eye plasma distribution ratio is 0.02. Over 90% of all patients in the phase 3 clinical trials had concentrations of the parent compound, tazarotene, <1ng/ mL with the highest being 6ng/ mL.

Oral delivery of 1.1 mg and 6 mg multiple doses led to 28.9 ng/ mL and 227 ng/ ml peak levels with a 2.56 ng/ mL trough. This corresponds to a maximum possible 4 ng/ mL ocular level for the highest dose. Figure 11 depicts the tissue distribution of tazarotenic acid. The eyes show a 2% tissue/ plasma ration in the rat. It should be noted that tazarotenic acid is 99% protein bound and distribution is limited to unbound drug. Hence, the overwhelming majority of ocular tazarotenic acid concentrations are most probably in the anterior tissues. Further, the log P of tazarotenic acid is calculated to be 2.53 hence it is not expected to display efficient penetration of the blood-retinal barriers.

TABLE 3. RETINOID LIPOPHILICTY AND SIDE EFFECTS

Compound	Bexarotene	Acetretin	Isotretinoin
Chemical Structure			
log P [1]	8.75	5.73	6.83
log D [1] pH 7.4	5.93	3.14	4.25
Cataract	Yes	Yes	Yes
Night Blindness	Yes	Yes	Yes
Pseudotumor Ceribri	Yes	Yes	Yes
Depression	Yes	Yes	Yes
Nervousness/ Agitation	Yes	Yes	Yes
Compound	**Tazarotene**	**Tazarotenic Acid**	
Chemical Structure			
log D [1] pH 7.4	6.21 (4.30 measured)	2.52	
Cataract	N/A [2]	No	
Night Blindness	N/A [2]	No	
Pseudotumor Ceribri	N/A [2]	No	
Depression	N/A [2]	No	
Nervousness/ Agitation	N/A [2]	No	

1. Calculated values, ACD/PhysChem computer software (v5.0)
2. Converted to tazarotenic acid upon absorption.

The foregoing compounds of the present example may be provided in any of the intraocular implants described herein.

Example 7

Targeted Retinal Drug Delivery by Subconjunctival and Periocular Administration of Sustained Delivery Systems.

This example describes the subconjunctival and periocular administration of compounds providing for higher retinal concentrations than obtained from immediate release or direct intraocular administration. It has been observed that compounds penetrating the RPE develop higher retinal/ vitreous concentration ratios than when delivered by intraocular administration. More significant is the fact that controlled or sustained delivery from the subconjunctival route results in significantly higher retinal/ vitreous ratios than non-controlled delivery.

This example demonstrates improvements in pharmacotherapy of drugs directed at the posterior ocular structures. This example describes (i) use of sustained or controlled, subconjunctival or periocular, administration of drugs to target choroid, RPE and retinal drug delivery; (ii) use of PLGA microspheres to sustain or control, subconjunctival or periocular, administration of drugs resulting in higher retina/ vitreous concentration ratios; (iii) use of monolithic PLGA implants to sustain or control, subconjunctival or periocular, administration of drugs resulting in higher retina/ vitreous concentration ratios; (iv) use of bioerodible controlled delivery systems to sustain or control, subconjunctival or periocular, administration of drugs resulting in higher retina/ vitreous concentration ratios; (v) use of non-bioerodible controlled delivery systems to sustain or control, subconjunctival or periocular, administration of drugs resulting in higher retina/ vitreous concentration ratios; (vi) currently, the only methods for achieving therapeutic retinal concentrations of drugs includes high dose systemic administration or direct intraocular implantation or injection. This examples provides more efficient choroid, RPE and retinal delivery of drugs and thereby allows for improvements in their therapeutic index.

As discussed herein, delivery of drugs to the retina, vitreous and uveal tract is typically achieved by high systemic dosing or direct intra-ocular injections. This example shows that the retinal/ vitreal drug concentration ratio for compounds delivered from intraocular injection or non-sustained release subconjunctival administration is relatively low. In contrast, delivery of compounds to the retina from sustained subconjunctival administration results in a dramatic increase in the retinal/ vitreous concentration ratio of drugs (See Table 4).

Compounds are eliminated from the vitreous by diffusion to the retro-zonular space with clearance via the aqueous humor or by trans-retinal elimination. Most compounds utilize the former pathway while lipophilic compounds and those with trans-retinal transport mechanisms will utilize the latter. In both cases the result is a relatively low retinal/ vitreous concentration ratio of drug. Penetration of drug from periocular administration can proceed by trans-scleral diffusion with penetration through the RPE or diffusion to the iris root followed by posterior diffusion of drug into the vitreous. With pulsatile dosing the result is a relatively low retinal/ vitreal concentration gradient. In this example we show that by utilizing sustained or controlled drug delivery systems we can achieve higher retinal/ vitreal drug concentration ratios. Sustained delivery allows the eye to develop and maintainsteady-state rate processes. The result includes (i) a targeting of the drug to the retina over the vitreous; (ii) a lower vitreous concentration for a given retinal level relative to other routes of delivery; (iii) improved efficacy for compounds acting at the choroid, RPE or retinal; and (iv) potential reduction in intraocular side effects due to reduced vitreous levels.

Briefly, albino rabbits were dosed via intraocular injection with 1.25 μg of tazarotene or tazarotenic acid. Injection was made mid-vitreous. After dosing the vitreous, retina and aqueous humor concentrations of tazarotene and tazarotenic acid were determined at 0.5, 1, 2, 4, 8, 12 and 24 hours post dosing.

Tazarotene was also dosed in the subconjunctival space. Three dosage forms were evaluated: A tazarotene aqueous suspension (1 mg), a tazarotene subconjunctival olive oil solution (1 mg), and a tazarotene poly (lactide-co-glycolide) microsphere suspension. After dosing, the vitreous, retina and aqueous humor concentrations of tazarotene and tazarotenic acid were determined at 2, 8, 24, 48, 96, 168 and 336 hours post dosing.

The mean retinal/ vitreal concentration ratio as well as the retinal/ vitreal $AUC_{0-24tlast}$ ratio are given in Table 4. The data show a higher retinal/ vitreous ratio for tazarotene delivered from sustained release. This is graphically depicted in Figure 12. A higher ratio of tazarotene in the retina is achieved with sustained release when compared with both non-sustained subconjunctival or direct intraocular administration. Thus, this examples provides implants and methods for (i) targeting of the drug to the retina over the vitreous; (ii) a lower vitreous concentration for a given retinal level relative to other route of delivery; (iii) improved efficacy for compounds acting at the choroid, RPE or retinal level; or (iv) potential reduction in intraocular side effects due to reduced vitreous levels relative to the retina.

Table 4. **Vitreous Concentrations of TAZAROTENE and TAZAROTENIC ACID after Intravitreal and Subconjunctival Dosing.**

Dosage Form	Intravitreal Injection (1.25 μg)	Subconj. Suspension (1 mg)	Subconj. Oil Solution (1 mg)	Subconj. Microsphere s (1 mg)
Mean Retinal Concentration TAZAROTENE (ng/ mL)	493.4	57.1	387.4	287.0
Mean Vitreous Concentration TAZAROTENE (ng/ mL)	417.0	42.0	96.2	21.9
Retinal/ Vitreous Concentration Ratio	**1.18**	**1.36**	**4.18**	**13.1**
Mean Retinal AUC TAZAROTENE (ng*hr/ mL)	8465	17000	127000	90100
Mean Vitreous AUC TAZAROTENE (ng*hr/ mL)	8611	6880	23400	4650
Retinal/ Vitreous AUC Ratio	**0.98**	**2.47**	**5.43**	**19.38**

Example 8

Tazaratene wafer implants with additives

Tazaratene wafers were prepared by mixing tazarotene, RG 752 & the additive (Solutol®, Kollidon®, or Lutrol®). The additive may be a polyvinyl acetate. The powder mixture was melted and poured into a polymer melt. This was then compressed to the desired thickness & cut with a 2.5 mm trephine. These wafers are biodegradable drug delivery systems with improved mechanical properties and tailored release rates especially well suited for subconjunctival ocular drug delivery, as shown in Figure 13.

Wafers prepared without the additives may be too brittle or fragile to cut, isolate, depending on the drug load and the polymer used. The additives may act as lubricants that make the wafers less brittle under the same processing conditions and thus reduces loss due to breakage and increase the yield. The choice and amount of additive used can tailor to the drug release rate, either accelerate or decelerate the release rate.

Example 9

Tazarotene drug delivery system with blended polymers

Tazarotene implants were prepared by mixing tazarotene and polymers RG502H with R202H or RG502H with RG752. The powder mixture was melted, pelletized, and extruded at specified temperatures depending on the drug load and polymer mix ratio. The implants provide a more predictable and linear release profile that can be achieved by adjusting the polymer blend ratio, as shown in Figure 14. One of the benefits is to alleviate or reduce the typical sigmoidal release curve obtained with only one polymer.

Example 10

Tazarotene containing intraocular implants

The intended delivery was for 3–6 months with an initial drug load of 0.1mg – 0.5 mg per implant. Four different polymers, RG502, RG502H, RG752, and R202H were used to formulate Tazarotene. Formulation #9, 50% Tazarotene (500 μg dose) in RG752 was selected for further studies. Implants were also made which contained 50 μg of tazarotene. Also discussed herein are formulations having a more linear release using polymer blends and wafer formulations with additives to improve their mechanical properties.

The initial Tazarotene PLGA (PLA) intra-ocular implant was intended for a 3-6 month delivery with a drug load of 0.1 to 0.5 mg. Two methods of preparing tazarotene implants were used, polymer melt and powder compaction. The former method involved first mixing the polymer with Active Pharmaceutical Ingredient (API), then melting the resulting powder blend at a temperature lower than the melting point of API to prevent its decomposition, and finally extruding the API polymer blend into filaments. The latter method was performed by first mixing the polymer with API, then compacting the powder blend into the extrusion barrel, and finally heating the barrel and extruding the filaments. The polymer melt method may be preferred over the powder compaction method since the latter can create a dust cloud during compaction process. Extruded filaments were then cut to the appropriate weight of 1 mg +/- 10% as rod-shaped implants or drug delivery systems (DDSs).

Due to the low melting point of Tazarotene (m.p. = 103-106°C), only polymers with molten range below Tazarotene's melting point could be effectively used in the process. Of the polymers available, only the ones with an inherent viscosity (I.V.) of 0.2 dl/g or lower were selected. Polymers with higher inherent viscosities become molten at temperatures higher than the melting point of Tazarotene and could cause degradation of tazarotene.

A second geometry used in making the Tazarotene DDS was the wafer. It was believed that this configuration could be more easily implanted subconjuntivally than the rod. The wafer process was performed by taking the melted polymer blend and compressing it into the desired thickness, then cut into 2.5 mm diameter disc weighing 1 mg each. Various processing aids were investigated in order to improve the cutting process.

MATERIALS AND METHODS:

The implant was either a rod (2 mm L x 0.72 mm diameter) or a wafer (0.13 mm thickness x 2.5 mm diameter) drug delivery system (DDS) each weighing

between 900 μg to 1100 μg. In each formulation Tazarotene was combined with the polymer in a stainless steel mortar and mixed via the Turbula shaker set at 96 RPM for 15 minutes, the powder blend was scraped off the wall of the mortar and then remixed for an additional 15 minutes. The mixed powder blend was heated to a semi-molten state at 95 °C for a total of 30 minutes, in three 10-minute intervals, forming a polymer/drug melt. The polymer/drug melt was pelletized using a 9 gauge polytetrafluoroethylene (PTFE) tubing, loaded into the barrel and extruded at the specified core extrusion temperature into filaments, then cut into 1 mg size DDS. Alternatively, the polymer melt was flattened with the Carver press at a specified temperature and cut into 2.5 mm wafers, each weighing 1 mg.

The in-vitro release testing was performed on each lot of implant (rod or wafer) in three replicates initially, and later in six replicates. Each implant was placed into a 40 mL screw cap vial with 35 mL of saline solution containing various amount of Tween-80 at 37 °C. Thirty mL aliquots were removed and replaced with equal volume of fresh medium on day 1, 4, 7, 14, 28, and every two weeks thereafter. The drug assays were performed by HPLC, which consists of a Waters 2690 Separation Module (or 2696), and Waters 2996 Photodiode Array Detector. A Phenomenex Luna C8 (2), 3 μm; 4.6 x 100 mm column was used for separation and detector was set at 325 nm. The mobile phase was (60:39.8:0.2) acetonitrile-H_2O-CH_3COOH with flow rate of 1 mL/min and a total run time of 15 min per sample. The release rates were determined by calculating the amount of drug being released in a given volume of medium over time in μg/day.

RESULTS AND DISCUSSION:

Initial Dose (100-700 μg) Tazarotene Formulations

The polymers chosen were Boehringer Ingelheim Resomer RG502, RG502H, RG752, and R202H. RG502 is (50:50) poly(D, L-lactide-co-glycolide), RG502H is (50:50) poly(D, L-lactide-co-glycolide) with an acid end group, RG752 is (75:25) poly(D, L-lactide-co-glycolide), and R202H is 100% poly(D,L-lactide). All have an

inherent viscosity of 0.2 dl/g and can become molten at approximately 90-95 °C. The average molecular weight of Resomer RG502, RG502H, RG752 and R202H are 11700, 8400, 11200, and 6500 daltons, respectively.

Preliminary data obtained from the in-vitro release testing of the first eight formulations in 0.9% saline showed no drug release for the first two weeks. This was due to the extremely low solubility of Tazarotene in 0.9% saline, which was determined to be less than 1 μg/mL. Therefore, it was difficult to see any differences in the release profiles of different formulations. Work began to search for a release medium that would differentiate the release profiles of all formulations. It was found that the solubility of Tazarotene could be increased by the addition of Tween-80 in 0.9% saline. Comparing the various Tween-80/saline solutions tested (0.25%. 0.5%, 0.75%, and 1%) the 0.5% Tween-80 in saline provided the most stable and predictable release curve, and thus it was used as the medium for all subsequent release testing. The release testing of those eight formulations that showed no release in 0.9% saline was restarted using 0.5% Tween-80 in saline as the release medium.

Implants were formulated Tazarotene with the four polymers with varying amounts of drug loads from 10 to 50% (Formulation # 1-14), as shown in Table 5. Based on the release data, other formulations (Formulation # 15-28) were subsequently manufactured with adjustments or modifications. Release data from the first 24 formulations (1-2, 3-19, 22, 24-28) were collected on the designated days and were then compiled based on the polymer, shown in Figures 15A, 15B, 15C, and 15D. In theory, there is a general correlation between drug load and release rates; higher drug load yields faster release.

Table 5. Tazarotene Formulation (100 – 700 μg)

Formulation #	Taz	Polymer	I.V.	Extru T	Nozzle	Weight
1	50%	RG502H	0.2	87 °C	720 μm	1 mg
2	25%	RG502H	0.2	81 °C	720 μm	1 mg
3	10%	RG502H	0.2	78 °C	720 μm	1 mg
4	50%	RG502	0.2	91 °C	720 μm	1 mg
5	25%	RG502	0.2	84 °C	720 μm	1 mg
6	10%	RG502	0.2	80 °C	720 μm	1 mg
7	20%	RG502	0.2	84 °C	720 μm	1 mg
8	35%	RG502	0.2	88 °C	720 μm	1 mg
9	50%	RG752	0.2	86 °C	720 μm	1 mg
10	35%	RG752	0.2	82 °C	720 μm	1 mg
11	20%	RG752	0.2	79 °C	720 μm	1 mg
12	50%	R202H	0.2	81 °C	720 μm	1 mg
13	35%	R202H	0.2	76 °C	720 μm	1 mg
14	20%	R202H	0.2	74 °C	720 μm	1 mg
15	60%	RG502H	0.2	91 °C	720 μm	1 mg
16	70%	RG502H	0.2	97 °C	720 μm	1 mg
17	50%	RG502H	0.2	n/a	wafer	1 mg
18	50%	RG502	0.2	n/a	wafer	1 mg
19	50%	RG752	0.2	n/a	wafer	1 mg
20	50%	R202H	0.2	n/a	wafer	1 mg
21	35%	R202H	0.2	n/a	wafer	1 mg
22	35%	RG502H	0.2	82 °C	720 μm	1 mg
23 (repeat 15)	60%	RG502H	0.2	91 °C	720 μm	1 mg
24	60%	RG502	0.2	96 °C	720 μm	1 mg
25	60%	RG752	0.2	91 °C	720 μm	1 mg
26	60%	RG502H	0.2	n/a	wafer	1 mg
27	60%	RG502	0.2	n/a	wafer	1 mg
28	60%	RG752	0.2	n/a	wafer	1 mg
29 (repeat 1)	50%	RG502H	0.2	87 °C	720 μm	1 mg
30 (repeat 17)	50%	RG502H	0.2	n/a	wafer	1 mg
31	Placebo	RG502H	0.2	72 °C	720 μm	1 mg
32	Placebo	RG502H	0.2	n/a	wafer	1 mg
33	Placebo	R202H	0.2	74 °C	720 μm	1 mg
34	Placebo	RG752	0.2	79 °C	720 μm	1 mg

Different polymers yielded different release rates; RG502H and RG502 yielded a maximum of three to four months release, depending on the drug load, RG752 yielded a maximum of four to six months release, and R202H yielded upwards of six months release and longer. Formulation # 17 (50% Taz / RG502H

wafer), formulation # 5 (25% Taz / RG502), formulation # 8 (35% Taz / RG502), formulation # 18 (50% Taz / RG502 wafer), formulation # 9 (50% Taz / RG752), and formulation # 28 (60% Taz / RG752 wafer), all exhibited fairly linear release curves that gave three to six-months release.

Three rods and three wafers DDSs, were selected to study in-vitro release study using bovine vitreous humor (BVH). The DDS formulations selected were #1, 4, 9, and the wafer formulations selected were #17, 18, and 19. The release profiles of the six formulations are shown in Figure 16.

Formulation #1 yielded a cumulative Tazarotene release of 80 % and leveled off after 71 days, while its wafer counterpart (formulation #17) yielded a cumulative release of 91 % and leveled off after 97 days. Formulation #9 yielded a cumulative release of 77 % and leveled off after 155 days, while its wafer counterpart (Formulation #19) yielded a cumulative release of 94 % after 126 days. Finally, formulation #4 reached its maximum Tazarotene release of 96 % after approximately 71 days, while its wafer counterpart (Formulation #18) reached its maximum Tazarotene release of 82% after 97 days.

Formulations #1, 9, 12, #17 were studied further. The in-vitro release profiles of these 4 formulations are shown in Figure 17. Formulation # 9 was studied further Preliminary analysis on product Potency and Content Uniformity before sterilization were 98% and 100.5% ± 5% of Label Strength, respectively, and product Potency and Content Uniformity after sterilization were 96.6% and 96.9% ± 3.9% Label Strength, respectively, as shown in Table 6.

Table 6. Content Uniformity and Assay of Tazarotene GLP Lot # 229-01

Content Uniformity and Assay Before Sterilization				Content Uniformity and Assay After Sterilization			
Assay	**μg/mL**	**μg/10 dds**	**% Potency**	**Assay**	**μg/mL**	**μg/10 dds**	**% Potency**
Taz-Assay-1	49.19	4919	98.38	Taz-Assay-1	47.88	4788	95.76
Taz-Assay-2	48.76	4876	97.52	Taz-Assay-2	48.75	4875	97.50
% Mean			**98.0**	% Mean			**96.6**
Content Uniformity				**Content Uniformity**			
Taz-CU-1	51.27	512.7	102.54	Taz-CU-1	45.68	456.8	91.36
Taz-CU-2	50.17	501.7	100.34	Taz-CU-2	51.00	510.0	102.00
Taz-CU-3	54.20	542.0	108.40	Taz-CU-3	48.89	488.9	97.78
Taz-CU-4	51.55	515.5	103.10	Taz-CU-4	49.85	498.5	99.70
Taz-CU-5	46.50	465.0	93.00	Taz-CU-5	45.42	454.2	90.84
Taz-CU-6	50.71	507.1	101.42	Taz-CU-6	47.51	475.1	95.02
Taz-CU-7	46.44	464.4	92.88	Taz-CU-7	49.76	497.6	99.52
Taz-CU-8	51.03	510.3	102.60	Taz-CU-8	48.27	482.7	96.54
Taz-CU-9	48.27	482.7	96.54	Taz-CU-9	47.74	477.4	95.48
Taz-CU-10	52.31	523.1	104.62	Taz-CU-10	50.36	503.6	100.72
% Mean			**100.5**	**% Mean**			**96.9**
% RSD			**5.0**	**% RSD**			**3.9**

The release profiles of the GLP lot and the stability lots (stored at 40 °C / 75% RH and 25 °C / 60 % RH for one month) are shown in Figure 18.

Lower Dose (50 μg) Tazarotene Formulations

Lower dose implants were formulated with 1/10th the dose of Tazarotene (i.e. 50 μg). Since the original implant (Formulation # 9) was 50% Tazarotene in RG752 polymer, the same drug to polymer ratio was used to achieve similar release profiles. Therefore the size of the implant needed to be reduced. In order to accomplish this, the diameter of the filament was reduced from the original 720 μm down to a smaller diameter. The formulations for lower dose Tazarotene implants are shown in Table 7.

Table 7. Tazarotene Formulation - Lower Dose (50 μg)

Formulation #	Taz	Polymer	I.V.	Extru T	Nozzle	Weight
47	50%	RG752	0.2	90 °C	380v μm	0.1 mg
48	50%	RG752	0.2	92 °C	450 μm	0.1 mg
49	50%	RG752	0.2	96 °C	300 μm	0.1 mg
50	50%	RG752	0.2	90 °C	720 μm	1 mg
51	40%	RG752	0.2	88 °C	380v μm	0.125 mg
52	40%	RG752	0.2	90 °C	450 μm	0.125 mg
53	40%	RG752	0.2	96 °C	300 μm	0.125 mg
54	40%	RG752	0.2	90 °C	380 μm	0.125 mg
58	30%	RG752	0.2	94 °C	300 μm	0.16 mg
59	30%	RG752	0.2	88 °C	450 μm	0.16 mg
60	30%	RG752	0.2	88 °C	380 μm	0.16 mg
61	30%	RG752	0.2	88 °C	380v μm	0.16 mg
62	25%	RG752	0.2	88 °C	380 μm	0.2 mg
63	25%	RG752	0.2	89 °C	380v μm	0.2 mg
64	25%	RG752	0.2	89 °C	450 μm	0.2 mg
65	25%	RG752	0.2	94 °C	300 μm	0.2 mg

For these implants, four different nozzle diameters were used, 300 μm, 380 μm, 380v μm, and 450 μm. The difference between 380 and 380 v is that the inlet of the former has a shallow groove and the latter has a v-groove. Release data taken showed that within the same drug load, there were no significant differences among the DDS prepared with 300 μm, 380 μm, 380v μm, or 450 μm diameter nozzles, as shown in Figure 19 and Figure 20.

Formulations #49 and #53 and their corresponding placebos, and one regular dose wafer formulation, #17 (wafer, 1 mg) plus its placebo were studied further. Formulation #49 was 50% Taz/RG752 with filament diameter of 300 μm, and formulation #53 was 40% Taz/RG752 also with filament diameter of 300 μm. As shown in Figure 21, both formulations have release rate slightly faster than the GLP lot up to day 105 releasing 46% and 40% for #49 and #53, respectively, while the GLP lot released 40%. On day 137, formulation #49 and formulation #53 were releasing 56% and 52%, respectively, while the GLP lot was releasing 77% at approximately the same time. In contrast, formulation # 17 was by far the fastest of all four, releasing up to 91% after 97 days.

Additional 500 μg Tazarotene formulation: Linear Release Profile

After the completion of the GLP lot of formulation #9, an effort was started to formulate Tazarotene with more linear release profiles. One approach was to combine two different polymers with Tazarotene. The selection of the two polymers was meant to compliment the release profile of Tazarotene with each individual polymer. An example of a potential blend was to use polymers RG502H and R202H, and RG752. Their individual release profile is shown in Figure 22. Tazarotene formulated with RG502H reached a maximum of 81% after 85 days, while Tazarotene formulated with RG752 reached a maximum of 74% after 181 days, and Tazatotene formulated with R202H was much slower and it reached 90% after 269 days.

Three different blends of Tazarotene / R202H / RG502H with the ratio of (50:40:10), (50:30:20), and (50:25:25) were made. Likewise, three different blends of Tazarotene / RG752 / RG502H with the ratio of (50:40:10), (50:30:20), and (50:25:25) were made. The release profiles are shown in Figures 23A and 23B.

In Figure 23A, the graph clearly showed that the release profiles of the three different blends of RG752 and RG502H were in between the release profile of Taz with RG752 and that of Taz with RG502H. Furthermore, up to day 100, the blend containing more RG502H released at a faster rate than the blend containing less RG502H. In Figure 23B, the release profiles of the blends were in between the release profiles of Taz with R202H and Taz with RG502, up to day 60, and then the profiles of the blend continued their release at near zero order kinetics. Again, the blend with more RG502H released at a faster rate. It is interesting to note that linearity was achieved using RG502H and R202H, which are PLGA and PLA, respectively. The combination of RG502H and RG752 was not as successful at obtaining a more linear profile considering the release profiles of formulation #9 and formulation #12 were somewhat similar.

Additional Wafer Formulations: Addition of processing aids.

During fabrication of Tazarotene wafers, it was noticed that some formulations (#20 and #21) were too fragile or brittle to process (each wafer has a thickness of 0.005 inch or 0.127 mm and a diameter of 2.5 mm), while the others could be made but with losses up to 50% or more. Therefore, we decided to use processing aids that can change the mechanical properties of the wafers, making them less brittle. Solutol®, Kollidon®, and Lutrol®, excipients commonly used in many oral dosage forms, were our first 3 candidates. Solutol is polyethylene glycol 660 12-hydroxystearate, Kollidon (12 or 17) is polyvinyl-pyrrolidone, and Lutrol is a copolymer of polyethylene glycol and polypropylene glycol. All three additives when added to Tazarotene formulations led to wafers that were less brittle, much easier to manufacture and with higher yields. The release profiles of wafers made with these additives are shown in Figure 24.

Similar release profiles were obtained for Formulation 67 and formulation 68 when compared to formulation #57, while formulation #66 showed a more linear and slightly faster release profile.

CONCLUSIONS:

Over 30 different Taz formulations were prepared using low inherent viscosity poly (D,L- lactide-co-glycolide) / poly (D,L-lactide) polymers. Their release profiles were monitored in 0.5% Tween-80 in saline at 37 °C. Tazarotene (Formulation # 9, 50:50 Taz/RG752), with Resomer RG752 poly (lactide-co-glycolide) from Boehringer Ingelheim provided close to six months in-vitro continuous drug release profile. The Tazarotene implants weighed approximately 1 mg each and contained 500 μg of active pharmaceutical ingredient. The implants passed the Potency (96.6%) and Content Uniformity (96.9% ± 3.9%) specifications and have good stability. Implants with one-tenth dosage as the original formulation (implant with 50 μg of API), new Tazarotene formulations with a more linear release than formulation #9, as well as

Tazarotene wafers with additives as processing aids were also manufactured and studied.

Example 11

Retinoid-containing intraocular implants and proliferative vitreoretinopathy

PLA and PLGA implants 1.5 mm in diameter and 3 mm in length were fabricated by extrusion of the polymer drug blend. Tazarotenic acid (the free acid of Tazarotene) Tazarotene and 13-*cis*-retinoic acid were loaded into the implants at 10% concentrations. Briefly, pigmented rabbits were vitrectomized followed by intravitreal injection of 500,000 human RPE cells. After injection of the RPE cells the retinoid implants were placed into the vitreous and anchored to the sclera with the suture used to close the sclerotomy.

The eyes were examined weekly for 4 weeks. Severity of PVR was graded based on the Fastenberg scale. At 4 weeks gross pathology and limited histopathology were conducted. At 28 days only 12% of the Tazarotene and Tazarotenic acid treated eyes progressed to traction retinal detachment and 22% of the acutane treated eyes progressed. This is in comparison to 94% of the control eyes experiencing stage 3 or greater tractional detachment. This study clearly demonstrated the efficacy of the Tazarotene implants in this animal model. Gross pathology and limited histopathology has shown a good safety profile for Tazarotene and its PLGA/PLA implant.

As shown in Table 2 and discussed in Example 6, for the most part tazarotene is not observed in the plasma after topical or oral administration. Facile hydrolysis by pre-systemic metabolism rapidly generates the free acid. Tazarotenic acid plasma concentrations (Cmax, maximal plasma level) from topical administration range from 0.25 ng/ mL to 12 ng/ mL. It is important to note that these are plasma concentrations and the eye plasma distribution ratio is 0.02. Over

90% of all patients in the phase 3 clinical trials had concentrations of the parent compound, tazarotene, <1ng/ mL with the highest being 6 ng/ mL.

Oral delivery of 1.1 mg and 6 mg multiple doses led to 28.9 ng/ mL and 227 ng/ ml peak levels with a 2.56 ng/ mL trough. This corresponds to a maximum possible 4 ng/ mL ocular level for the highest dose. Figure 11 depicts the tissue distribution of tazarotenic acid. The eyes show a 2% tissue/ plasma ration in the rat. It should be noted that tazarotenic acid is 99% protein bound and distribution is limited to unbound drug. Hence, the overwhelming majority of ocular tazarotenic acid concentrations are most probably in the anterior tissues. Further, the log P of tazarotenic acid is calculated to be 2.53 hence it is not expected to display efficient penetration of the blood-retinal barriers.

Subconjunctival Microspheres

Tazarotene PLGA microspheres loaded with 20% tazarotene were also administered subconjunctivally at a dose of 2 mg. The specific formulation tested is a 75:25 PLGA microsphere (Applied Polymer Technologies PLGA 75:25 inherent viscosity 0.67 dl/ gm, 20% tazarotene/ 80% polymer, dose 2mg). The release profile of these microspheres is depicted in Figure 25.

The intraocular pharmacokinetics of Tazarotene was assessed in female New Zealand White rabbits following a single intravitreal injection. The rabbits were dosed with bilateral intravitreal injections of Tazarotene (1250 ng in 50 μL). At 0.5, 1, 2, 4, 8, 12, and 24 hr post dose, animals were sacrificed and the aqueous humor, vitreous humor, and retina samples were analyzed. The Tazarotene concentration in the vitreous humor declined from 578 ± 77 ng/g at 2 hr post dose to 115 ± 33 ng/g by 24 hr post dose with a mean half-life ($t_{1/2}$) of 9.22 hr. The mean vitreal clearance (Cl) was estimated to be 0.123 mL/hr. The Tazarotene concentration in the retina was close to its vitreal concentration at all time points, declining from 859 ± 131 ng/g at 2 hr post dose to 93.1 ± 28.9 ng/g by 24 hr post dose. Elimination of Tazarotene from the retina had a similar mean $t_{1/2}$ of 7.63. It was shown that Tazarotene has a

relatively long intravitreal half-life and that the retinal concentration parallel the vitreous when given as a neat injection. However, despite a very low solubility the clearance of Tazarotene from the retina is fast enough to require sustained release for extended duration of action.

The pharmacokinetics of sustained release tazarotene implants was assessed. Based on the preliminary data of intravitrealy administered tazarotene a dose of 500 mg delivered over 6 months was chosen for sustained release. The vitreal clearance of tazarotene is 2.95 mL/ day, hence the desired release rate over the 6 month period of time is 3 μg/ day. Formulations 1 (F1), 9 (F9) and 12 (F12) have release rates of 1.8, 2.5 and 5.5 mg/ day, respectively (See Figure 16). Formulation 17 (F17) releases at a higher rate of 7 μg/ day as it is implanted subconjunctivally and must first penetrate the RPE to access the eye (see Figure 16).

A six-month intraocular pharmacokinetic study of these formulations was initiated in female New Zealand White rabbits. Tissues were assayed following surgical placement of the Tazarotene intravitreal implants. The rabbits received a single bilateral intravitreal implant; a 500 μg Tazarotene dose in a high (formulation #1), medium (formulation #9) or low (formulation #12) release rate formulation. Plasma, vitreous, lens, retina and aqueous humor was assayed on days 4, 8, 14, 21, 31, 57, 113 and 171. Tazarotenic acid, tazarotenic acid is the free acid of the tazarotene ethyl prodrug. Tazarotenic acid is generated rapidly in vivo from tazarotene due to esterases. Hence, tazarotenic acid is monitored in the pharmacokinetic studies. The data show that the implants were successful in sustaining the intravitreal concentrations of tazarotene for six months in vivo. The data from this study is summarized in Table 8 and Figures 26 through 29.

Table 8. Key pharmacokinetic parameters of TAZAROTENIC ACID in ocular tissues and plasma following a single implantation of TAZAROTENE are summarized in the table below:

PK Parameters	Aqueous Humor	Lens	Retina	Vitreous Humor	Plasma
Formulation #1 (PLGA/RG502H) – High Release					
C_{max}[a] (ng/mL or ng/g)	1.08 ± 0.88	102 ± 52.7	186 ± 60.2	110 ± 36.7	4.83
T_{max} (day)	31	57	21	31	21
$AUC_{0\text{-tlast}}$[a,b] (ng·day/mL or ng·day/g)	85.7 ± 26.7	8370 ± 2230	15900 ± 3640	8680 ± 1630	351± 37.3
Formulation #9 (PLGA/RG752) – Medium Release					
C_{max}[a] (ng/mL or ng/g)	3.37 ± 2.51	45.6 ± 10.5	115 ± 58.8	67.6 ± 40.2	3.22
T_{max} (day)	57	57	57	57	57
$AUC_{0\text{-tlast}}$[a,b] (ng·day/mL or ng·day/g)	175 ± 103	5490 ± 753	14100 ± 2830	6480 ± 2410	364 ± 28.9
Formulation #12 (PLA/R202H) – Low Release					
C_{max}[a] (ng/mL or ng/g)	0.173 ± 0.0788	61.4 ± 35.8	110 ± 36.3	75.3 ± 37.3	2.61
T_{max} (day)	171	113	171	171	171
$AUC_{0\text{-tlast}}$[a,b] (ng·day/mL or ng·day/g)	18.5 ± 3.69	5780 ± 2246	9570 ± 2910	4540 ± 1180	148 ± 58.7

a Mean ± SEM. Per formulation, N=2 rabbits (4 eyes and 2 plasma) at C_{max}; N=16 rabbits (32 eyes) for calculation of $AUC_{0\text{-tlast}}$.

b t_{last} was Day 57 for all tissues and plasma.

Based on this data a nominal concentration of approximately 1 mg/ mL was chosen as a design target. Tazarotene is a more potent RAR agonist and as such effective concentrations are much lower than 1 mg/ mL.

Fastenberg PVR rating Scale

The five stages of massive periretinal proliferation

Stage	Characteristics
1	Intravitreal membrane
2	Focal traction: localized vascular changes; hyperemia; engorgement; dilation; blood vessel elevation
3	Localized detachment of medullary ray
4	Extensive retinal detachment; total medullary ray detachment; peripapillary retinal detachment
5	Total retinal detachment; retinal folds and holes

(Fastenberg DM et al, *Am J Ophthalmol.* 1982; 93: 559-564.)

Retinal Degeneration Models

The objective of this study was to determine the efficacy of various retinoids in preventing retinal damage or improving retinal survival in rhodopsin mutant transgenic rat models of retinal degeneration. The overall goal of the research was to investigate potential photoreceptor survival in mutant rhodopsin transgenic rats using RAR α, RAR $\beta\,\gamma$, and RXR retinoid agonists.

The experimental design was straightforward. A compound was injected daily to line 3 and every two days for line 4 animals (i.p.) for a given period and animals were sacrificed at the end by CO_2 overdose followed immediately by vascular perfusion of mixed aldehydes. Two litters of rats were used:

1. <u>Transgenic S334ter-3 rats.</u> Line 3 bears a rhodopsin mutation S334ter. Animals of this line exhibit rapid photoreceptor degeneration in the second week after birth. Injection of a compound was given daily from PD 6 (post-delivery day 6) to PD 20.

2. <u>Transgenic S334ter-4 rats.</u> Line 4 bears a rhodopsin mutation S334ter. Animals of this line experience a 80% loss of photoreceptors by 60 days after birth. The ONL is reduced to one row of nuclei. Injection of a compound was given every other day from PD 25 to PD 60.

For the line 3 animals, treatment started at PD 6 and the endpoint was PD 20. For the line 4, injection began at PD 25 and ended at PD60 when eyes were harvested. Eyes were embedded in an Epon/Araldite mixture for sectioning at 1 μm thickness along the vertical meridian. Protection of photoreceptors was evaluated by counting the rows of nuclei in the outer nuclear layer.

The outcome was a measure of retinal outer layer thickness, and cytology over an 8 week period. Compounds included the retinoid agonists tazarotene (Compound A, RAR β γ), Compound C (RAR α) and Compound E (RXR). Tazarotene was the only compound to show efficacy, indicating an RAR β γ can protect photoreceptors in rhodopsin mutant rats. This is a fairly harsh model and as such the modest improvement by tazarotene is quite significant.

Light Degeneration Model

Compound D, Compound E, and tazarotene were evaluated in the blue light retinal degeneration model. Sprague dawley rats were pretreated for five days with daily oral doses of the retinoids. The rats were then exposed to high intensity light, 12000 lux blue fluorescent, for eight hours. Five days post exposure the retinal

function was assessed by full flash ERG and structure by outer nuclear layer thickness.

Tazarotene was shown to significantly protect both retinal function and structure. The RXR agonists were not shown to protect retinal function at concentrations below those required to maintain receptor selectivity.

Example 12

Manufacture and Properties of Tazarotene-containing Polymeric Microparticles

Polymeric microparticles were produced using poly (DL-lactide-co-glycolide) acid polymers (PLGA polymers). A first set of batches of microparticles comprised tazarotene and PLGA 50/50 (50% lactic acid and 50% glycolic acid) and PLGA 75/25 (75% lactic acid and 25% glycolic acid) obtained from Sigma Aldrich. The PLGA 50/50 had an inherent viscosity of between 0.55 and 0.75 dL/g. The PLGA 75/25 had an inherent viscosity of 0.69 dL/g. A second set of batches of microparticles comprised tazarotene and PLGA 75/25 obtained from Absorbable Polymer Technologies (APT). The APT PLGA 75/25 had an inherent viscosity (i.v.) from about 0.35 to about 0.55 dL/g at 30 degrees C in HFIP.

Batches of microparticles were produced by forming an emulsion from two separate compositions. A first composition contained methylene chloride (solvent), PLGA, and tazarotene. The second composition contained water and polyvinyl alcohol (PVA, stabilizer). The first and second composition were combined to form an emulsion. The emulsion was rinsed and centrifuged. The resulting material was then dried. In this method, the drying was performed using a vacuum oven at a temperature of 40 degrees Celsius.

In another method, the resulting material was dried using a freeze drying process.

Another method included a step of sterilizing the microparticles. Another method included a step of storing the microparticles in a package, at 25 degrees C, 30 degrees C, or 40 degrees C, with predetermined amounts of relative humidity.

It was observed that vacuum hot drying (40 degrees C) resulted in some product loss and aggregation of microparticles (FIG. 32). It was also observed that the presence of PVA in the pellet during the centrifugation process made it difficult to suspend the microparticles. Freeze drying the material resulted in a fine powder without aggregate formation, as shown in FIG. 32. Gamma sterilization (32-33 KG) resulted in formation of agregates and a yellow color developing (FIG. 33). Incomplete removal of methylene chloride resulted in aggregate formation.

Batches of microparticles were produced that included 0% tazarotene, 10% tazarotene, or 20% tazarotene. The 10% tazarotene batches were more homogenous than the 20% tazarotene batch. The maximum microparticle diameter for the non-sterilized microparticles was about 10 micrometers.

The aggregation observed upon gamma sterilization of the microparticles may be due to a temperature increase during the sterilization procedure, for example, a 5-10 degree C increase for 25 kGy irradiation. When sterilization was performed at a reduced temperature, such as below 5 degrees C, the microparticle diameter distribution was substantially equal between sterile and non-sterile microparticles, as shown in FIG. 34. Methods of sterilizing polymeric microparticles are described in U.S. Patent Pub. No. 2005/0003007 (Boix et al.).

In view of the observations noted above, another manufacturing method was invented.

This method comprises a step of completely evaporating or removing methylene chloride, the solvent, from the first composition (i.e, the composition containing PLGA and tazarotene). The method also comprises a step of sieving the

microparticles in a liquid environment as compared to sieving oven dried microparticles. The method also comprises a step of freeze drying the microparticle-containing material as opposed to oven drying the microparticle-containing material. In other words, the microparticle-containing material is dried at a temperature substantially less than 40 degrees C. FIG. 35 is a flow chart of such a method.

A detailed embodiment of this method is provided below.

A 3 gram batch of tazarotene-containing microparticles is produced as follows. The amount of tazarotene in these microparticles was 10%.

2.7 grams of PLGA 75/25 (i.v. 0.43 or 0.65) was put in a 250 mL capped Erlen flask with a magnetic bar. The dry PLGA was stirred. About 180 mL of methylene chloride was added to the PLGA in the flask and stirred until the PLGA was completely dissolved. Some methylene chloride was retained to rinse the weighing vessels and the flask during the process. 0.300 grams of tazarotene was added to the PLGA/methylene chloride composition to form a first composition, or Part 1 shown in FIG. 35.

In a second beaker, 1000 mL of water was heated to 80 degrees C. The water was stirred with a magnetic bar at about 400-500 rpm. PVA (30.0 grams) was sprinkled on the vortex side of the stirred water. Once the PVA was dispersed, the strring speed was reduced to about 200 rpm to avoid bubble formation while maintaining PVA in suspension. This second composition (Part 2 shown in FIG. 35) was heated for 15 minutes, and then allowed to cool to room temperature.

An emulsion was formed by stirring the second composition with a high shear impeller at approximately 500-600 rpm while taking care to avoid incorporating bubbles. The first composition was slowly added to the stirred second composition using a disposable pipette. After adding about 40 mL of the first composition, the solution thickened and formed an emulsion. As the solution thickened, the stirring

speed was increased to keep the solution surface moving. The first composition continued to be added while increasing the stirring speed as necessary without producing foam. The first composition container was rinsed with the remaining methylene chloride, discussed above, and added to the second composition. The combined composition was stirred at a high speed for an additional 5 minutes, and then the speed was decreased in order to have a slight surface movement. The combined composition was stirred for 2 days. After day 1, the emulsion became liquefied. Therefore, it was necessary to reduce the stirring speed to reduce foaming. After day 2, the amount of methylene chloride was determined in the final composition using a Drager tube.

When the methylene chloride was completely removed from the solution, by evaporation, the remaining microparticle preparation was rinsed using centrifugation. In particular, tubes were filled with 40 mL of the microparticle composition and centrifuged at 5000 rpm for 15 minutes. The supernatant was removed from the tubes by turning the tubes upside-down. The tubes were then refilled with the suspension. Before the next centrifugation, the pellet from the previous centrifugation was suspended by sonicating the composition for 10 minutes, and vortexing the composition for 1 minute. Sonicating and vortexing steps were repeated as desired to completely dissolve the pellet.

After the overall microsphere suspension was centrifuged, the tubes were filled with purified water to rinse the preparation. The supernatant was removed using vacuum extraction. The microsphere preparation was rinsed three times with water. The pellets of the different tubes were combined into a single tube. The final pellet in the single tube was suspended with a small amount of water, and the resulting suspension was passed through two superimposed filters into a filter bottom. This passing step is also understood to be a sieving step. The first filter had a pore size of 125 μm and the second filter had a pore size of 45 μm. The filters were rinsed with water, and the solution was collected in the filter bottom.

The collected solution was transferred to two cleaned centrifuge tubes. Additional water was added to obtain a desired volume, and rinsing was repeated using a centrifuge at 5000 rpm for 15 minutes. The contents of the two tubes were combined into one tube.

The final pellet was suspended in a small amount of water, and the suspension was placed in the filter bottom. The filter bottom was covered with the 125 μm filter to avoid potential projection during a lyophilization step. The apparatus containing the suspension was frozen at 50 degrees C, and then freeze dried for at least 12 hours at 0.4 mbar minimum pressure (400 Pa). Water was completely removed.

The remaining microparticle preparation was stored and protected from light and moisture.

Batches were packaged in Eppendorf amber tubes. About 150 mg of the microparticles were put in each tube. Each tube was placed in a double plastic pouch with dessicant, and sterilized by gamma radiation (32.3-33 kGy).

Batches were also made using the previous method but the final tazarotene content was 20% as compared to 10%.

Batches of microparticles, such as microspheres, produced with the method described above, and containing tazarotene visually appeared to be a slightly yellow to yellow powder. The 10% batch (i.e., 10% tazarotene) had a substantially homogenous content, whereas the 20% batch had a heterogenous content. Macroscopic appearance was determined in accordance with SOP STAB20. Microscopic appearance was determined by examining one drop of a microparticle containing sample at 20x, 60x, and 100x magnification. Particle sizes, such as maximum diameter and volume, were determined by suspending an aliquot of a microparticle sample in 1 mL of deionized water. 5 μL of Tween 80 was added, and

the combination was sonicated for 10 minutes and vortexed for 15 seconds. The particle size was measured using a Coulter LS230 device. High performance liquid chromatography (HPLC) was used to examine tazarotene and degradation products. The analytes were eluted from a Beckman Ultrasphere XL C_8 column using a mobile phase composed of acetonitrile/water/glacial acetic acid (50/49.5/0.5). Detection was performed by ultraviolet absorbance at 325 and 270 nm. Quantitation was based on peak areas at 325 nm for tazortene.

The release profile of tazarotene from the microparticles was performed using a dialysis bag and dissolution media comprising a buffer and ethanol mixture (69.9/30.1) at a pH of 7.4. Samples were monitored at 37 degrees C in a shaker water bath at approximately 110 rpm. At each time point, an aliquot of the sample is collected and replaced by fresh media.

FIG. 36 illustrates the photographic microscopic appearance of three batches of microspheres containing 0% (placebo), 10%, or 20% tazarotene with PLGA 75/25 (iv 0.43) in non-sterile and sterile states, and three batches of similar microspheres containing PLGA 75/25 (iv 0.65) in non-sterile and sterile states.

Microspheres in the 10% batch had a maximum diameter that is less than about 10 μm, and the majority of the microspheres had a maximum diameter of about 1.5 to about 1.7 μm. Microspheres in the 20% batch had a maximum diameter of about 14-15 μm, and the majority fo the microspheres had a maximum diameter of about 0.5 to about 0.8 μm.

The 21 day release profile for batches DL005, DL006, DL009, and DL010 (shown in FIG. 36) are provided in Table 9 below:

Table 9

Batch Number	Cumulative % tazarotene total release	Average % tazarotene release/day
DL005 (10%)	22.0 %	1.10 %
DL006 (20%)	11.2 %	0.56 %
DL009 (10%)	16.0 %	0.80 %
DL010 (20%)	12.8 %	0.64 %

FIG. 37 illustrates graphs of the dissolution profile trends for tazarotene (top panels), tazarotenic acid (bottom panels) and another retinoid (middle panels). Based on the cumulative % tazarotene total release values after 21 days of in vitro dissolution, the dissolution rate for the 10% batches (DL005 and DL009) appears higher than the 20% batches (DL006 and DL010).

After 3 months of storage at 25 degrees C or 30 degrees C at 40% plus or minus 5% relative humidity, the particle size and distribution were substantially identical to fresh microparticles. After 3 months of storeage at 40 degrees C at 20% plus or minus 5% relative humidity, aggregates were observed (FIGs 38 and 39). No changes in particle size or particle size distribution were observed for particles stored at 5 degrees C and no controlled relative humidity.

The dissolution profile for a batch of microspheres (DL003) containing PLGA 75/25 (iv 0.69 dl/g) and 10% tazarotene and stored for 3 months is shown in table 10 below and FIG. 40.

Table 10

	Cumulative % tazarotene total release	Average % tazarotene release/day
DL003/initial	25.2%	1.26%
DL003-25 C/3 months	10.8%	0.52%
DL003-30 C/3 months	22.3%	1.06%
DL003-40 C/3 months	8.2%	0.39%

The dissolution profile for a batches DL005, DL006, DL009, and DL010 described above and stored for 3 months is shown in table 11 below and FIG. 41.

Table 11

	Cumulative % tazarotene total release	Average % tazarotene release/day
DL005/Initial	22.0%	1.10%
DL005-5 C/3 months	12.4%	0.59%
DL005-25 C/3 months	Not performed	Not performed
DL005-30 C/3 months	13.0%	0.62%
DL006/Initial	11.2%	0.56%
DL006-5 C/3 months	6.4%	0.31%
DL006-25 C/3 months	Not performed	Not performed
DL006-30 C/3 months	6.9%	0.38%
DL009/Initial	16.0%	0.80%
DL009-5 C/3 months	14.0%	0.67%
DL009-25 C/3 months	12.1%	0.58%
DL009-30 C/3 months	9.8%	0.47%

	Cumulative % tazarotene total release	Average % tazarotene release/day
DL010/Initial	12.8%	0.64%
DL010-5 C/3 months	11.0%	0.52%
DL010-25 C/3 months	10.4%	0.50%
DL010-30 C/3 months	12.2%	0.58%

In view of the foregoing, no macroscopic appearance modifications were observed, batch DL003 contained aggregates when stored for one month at 40 C, and contained particles with irregular shapes after 2 months when stored at 25 C and 30 C, batches DL005 and DL010 did not appear modified from initial fresh microspheres, the microspheres of batches DL005 and DL010 had particle sizes within a desired target range, batch DL003 presents similar tazarotene trends at all temperatures, batches DL005 and DL010 after 3 months of storage, the tazarotene trends decrease for all storage conditions without the appearance of degradation products, and no signficant differences in dissolution profiles can be observed between the different storage conditions for the tested batches.

Differential scanning calorimetry (DSC) was used to obtain additional phsico-chemical characteristics of the polymers used in the present microspheres. DSC analysis was performed using a DSC7 Perken Elmer. A first temperature rise was performed from 25 C to 70 C at 5 K/min, followed by a temperature cooling from 70 C to 25 C at 10 K/min, and a second temperature rise from 25 C to 70 C at 5 K/min. The determination of the glass transition temperature was performed on the second temperature rise.

The glass transition temperatures for the polymers were from about 44.6 C to about 45.3 C depending on the molecular weight (inherent viscosity). The lower the molecular weight polymers had a lower glass transition temperature. The glass

transition temperature decreased proportionally with the tazarotene loading reflecting a plasticizing effect on the tazarotene.

Additional dissolution profile testing was performed on batch DL003 at 44 days. The results are shown in the graphs of FIG. 42. After 44 days of dissolution, about 41.5% of the total tazarotene was released with an average release per day of about 0.94%. These values correspond to about 47.2 μg of tazarotene being released per day from a 50 mg microsphere sample. Thus, a 50 mg microsphere sample is expected to releasee tazarotene for about 3.5 months.

FIG. 43 presents the cumulative % release of tazarotene and the average % release/day of tazarotene, as well as the tazarotene dose/day (μg) obtained after 252 days of dissolution. Using a double logarighmic regression, a complete release of tazarotene for 10% batches (DL005 and DL009) occurs from about 338 days to about 643 days, while the 20% batches (DL006 and DL010) exhibit a total release from about 685 days to about 890 days.

FIG. 44 illustrates scanned electron microscopic images of 10% and 20% tazarotene loaded microparticles. The 10% microparticles had smooth spherical shapes, and the 20% microparticles had dimpled surfaces similar to golf balls.

FIG. 45 illustrates the effect of gamma sterilization on the microspheres. As shown in the right panel, gamma sterilization results in aggregation of individual microspheres.

FIG. 46 illustrates an electron microscopic image of the microspheres after 21 days of dissolution and after 45 days of dissolution. At 21 days of dissolution, microspheres are still visible (left panel). At 45 days of dissolution, the microspheres appear melted and stuck together (right panel).

The electron microscopic images appear to provide similar results as the visual microscopic images described above.

All references, articles, publications and patents and patent applications cited herein are incorporated by reference in their entireties.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

We claim:

1. A biodegradable intraocular drug delivery system comprising:

a retinoid component and a biodegradable polymer matrix that releases drug at a rate effective to sustain release of an amount of the retinoid component from the drug delivery system for at least about one week after the drug delivery system is placed in an eye.

2. The system of claim 1, wherein the retinoid component comprises at least one of a retinoid and a retinoid precursor.

3. The system of claim 1, wherein the retinoid component includes an retinoic acid receptor agonist.

4. The system of claim 1, wherein the retinoid component includes a tazarotene, salts thereof, and mixtures thereof.

5. The system of claim 1, wherein the retinoid component includes a tazarotenic acid.

4. The system of claim 1, further comprising an additional ophthalmically acceptable therapeutic agent.

5. The system of claim 1, wherein the retinoid component is dispersed within the biodegradable polymer matrix.

6. The system of claim 1, wherein the matrix comprises at least one polymer selected from the group consisting of polylactides, poly (lactide-co-glycolides), derivatives thereof, and mixtures thereof.

7. The system of claim 1, wherein the system is sterile.

8. The system of claim 1, wherein the matrix comprises a poly (lactide-co-glycolide).

9. The system of claim 1, wherein the matrix comprises a poly(D,L-lactide-co-glycolide).

10. The system of claim 1, wherein the matrix releases drug at a rate effective to sustain release of an amount of the retinoid component from the drug delivery system for more than one month from the time the system is placed in the vitreous of the eye.

11. The system of claim 1, wherein the retinoid component is a tazarotene or tazarotenic acid, and the matrix releases drug at a rate effective to sustain release of a therapeutically effective amount of the tazarotene or tazarotenic acid for a time from about two months to about six months.

12. The system of claim 1, wherein the implant is structured to be placed in the vitreous of the eye.

13. The system of claim 1, wherein the retinoid is tazarotene or tazarotenic acid provided in an amount from about 40% by weight to about 70% by weight of the implant, and the biodegradable polymer matrix comprises a poly (lactide-co-glycolide) in an amount from about 30% by weight to about 60% by weight of the drug delivery system.

14. The system of claim 1 formed as a rod, a wafer, a plug, or a particle.

15. The system of claim 1 which is formed by an extrusion process.

16. A method of making a biodegradable intraocular drug delivery system, comprising the step of: extruding a mixture of a retinoid and a biodegradable polymer component to form a biodegradable material that degrades at a rate effective to sustain release of an amount of the retinoid from the drug delivery system for at least about one week after the drug delivery system is placed in an eye.

17. The method of claim 16, wherein mixture consists essentially of an RAR agonist and a biodegradable polymer.

18. The method of claim 16, further comprising a step of mixing the retinoid with the polymer component before the extrusion step.

19. The method of claim 16, wherein the retinoid component and the polymer component are in a powder form.

20. The method of claim 16, wherein the polymer component comprises a polymer selected from the group consisting of polylactides, poly (lactide-co-glycolides), and combinations thereof.

21. The method of claim 16, wherein the polymer component is substantially free of polyvinyl alcohol.

22. A medicament, which is a biodegradable intraocular drug delivery system, for improving or maintaining vision in an eye of a patient by placing the biodegradable intraocular drug delivery system in an eye of the patient, the drug delivery system comprising a retinoid component and a biodegradable polymer matrix, wherein the drug delivery system degrades at a rate effective to sustain release of an amount of the retinoid component from the drug delivery system effective to improve or maintain vision in the eye of the patient.

23. The medicament of claim 22, wherein the medicament is effective to treat a retinal ocular condition.

24. The medicament of claim 22, wherein the ocular condition includes proliferative vitreoretinopathy.

25. The medicament of claim 22, wherein the drug delivery system is placed in the posterior of the eye.

26. The medicament of claim 22, wherein the drug delivery system is placed in the eye with a trocar.

27. The medicament of claim 22, wherein the drug delivery system is placed in the eye with a syringe.

28. The medicament of claim 22, wherein a therapeutic agent is administered in addition to the retinoid component to the patient.

29. The medicament of claim 22, wherein the retinoid component includes at least one of tazarotene, tazarotenic acid, salts thereof, and mixtures thereof.

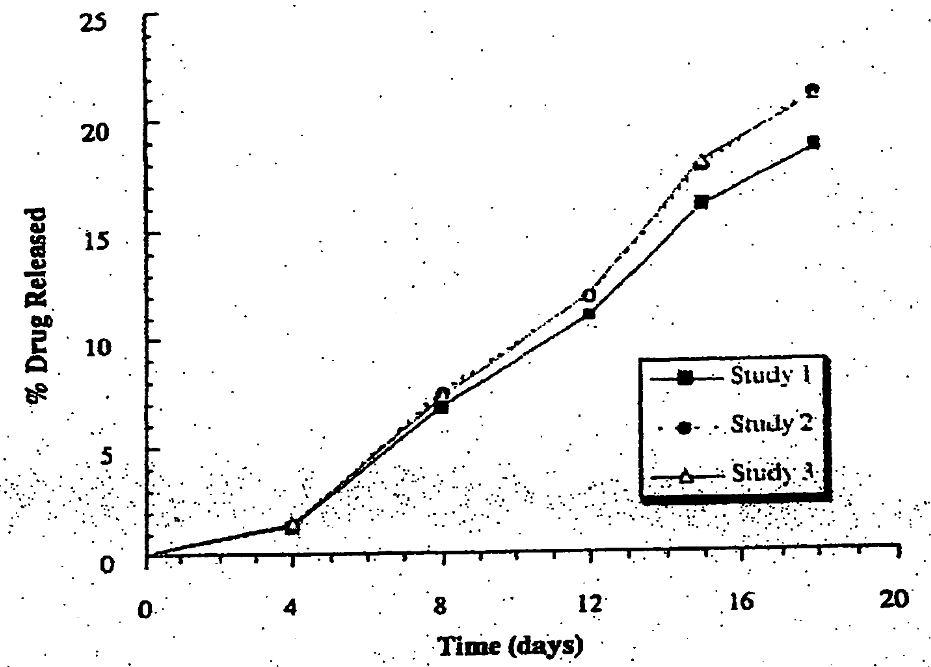

25
20
15
10
5
0
% Drug Released
0
4
8
12
16
20
Time (days)
Study 1
Study 2
Study 3

Fig. 1A

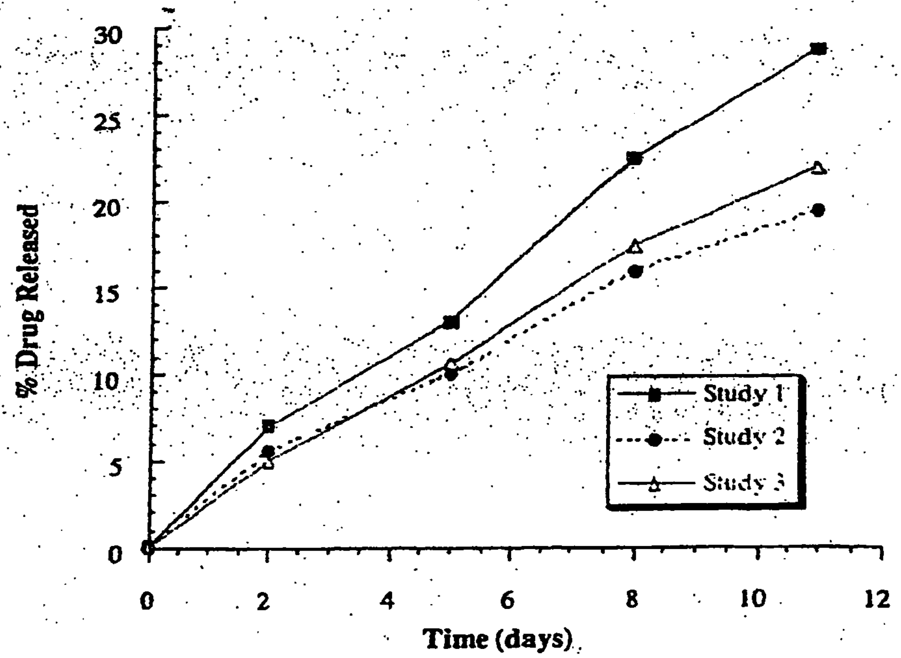

30
25
20
15
10
5
0
% Drug Released
0
2
4
6
8
10
12
Time (days)
Study 1
Study 2
Study 3

Fig. 1B

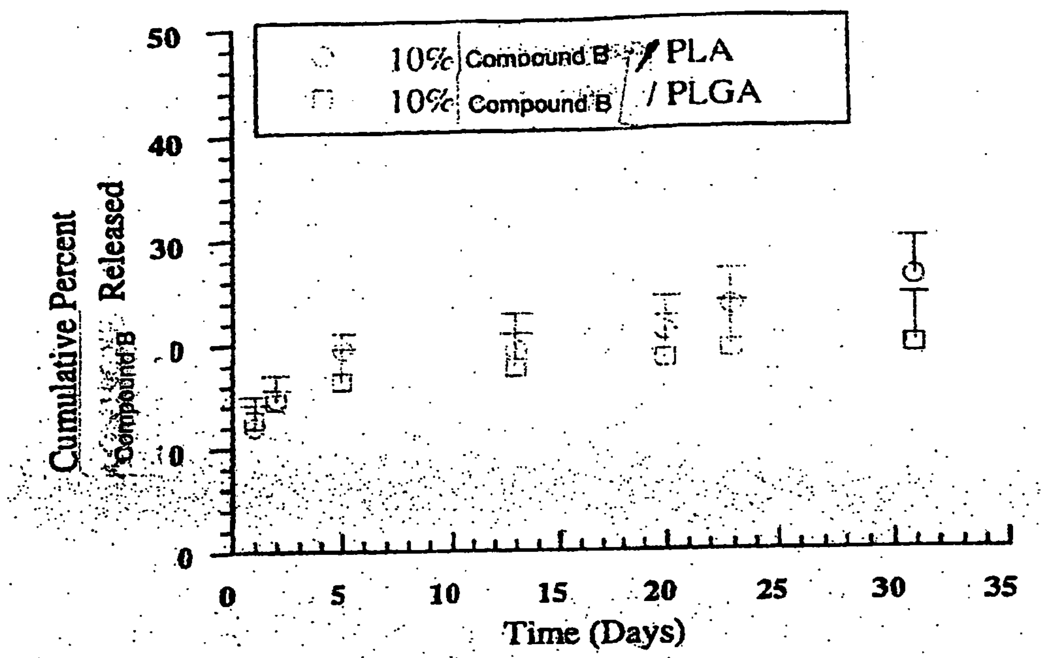

10% Compound B / PLA
10% Compound B / PLGA
Cumulative Percent Compound B Released
50
40
30
20
10
0
0
5
10
15
20
25
30
35
Time (Days)

FIG. 2

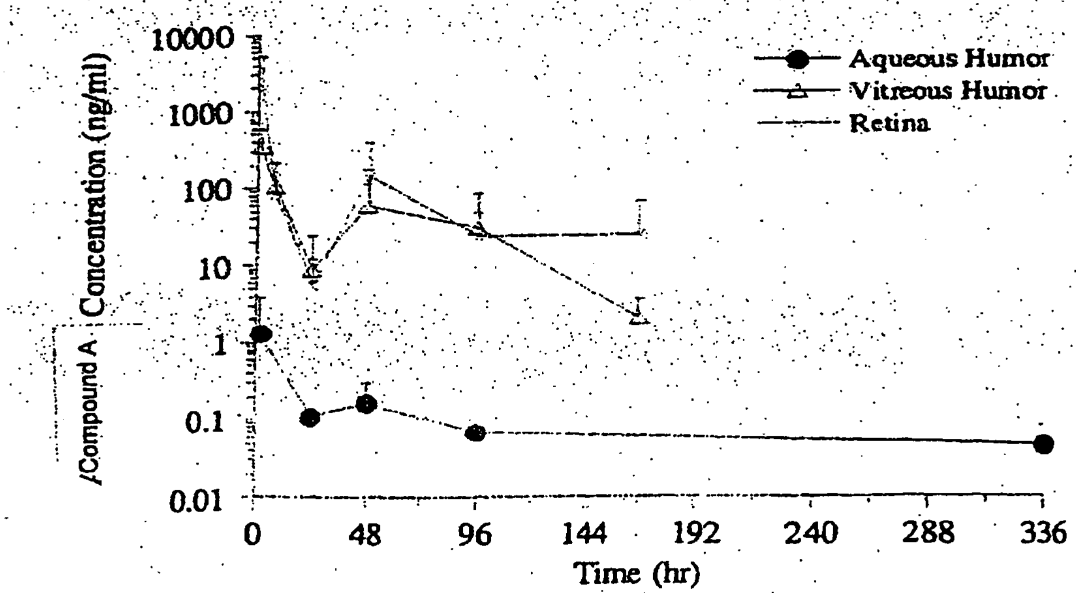

Aqueous Humor
Vitreous Humor
Retina
Compound A Concentration (ng/ml)
10000
1000
100
10
1
0.1
0.01
0
48
96
144
192
240
288
336
Time (hr)

FIG. 3

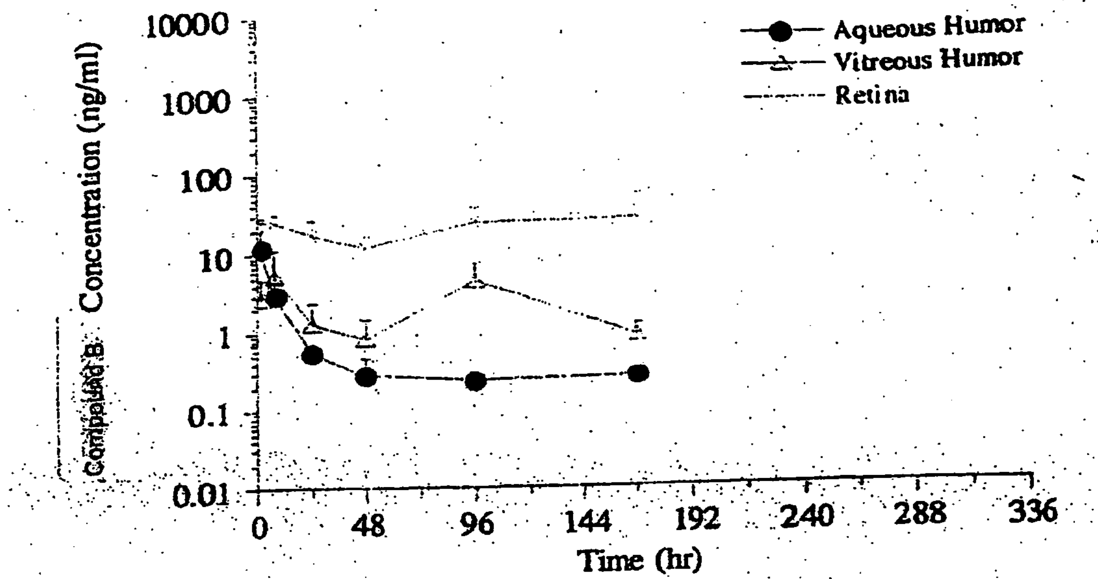

Aqueous Humor
Vitreous Humor
Retina
Compound B Concentration (ng/ml)
10000
1000
100
10
1
0.1
0.01
0
48
96
144
192
240
288
336
Time (hr)

Fig. 4

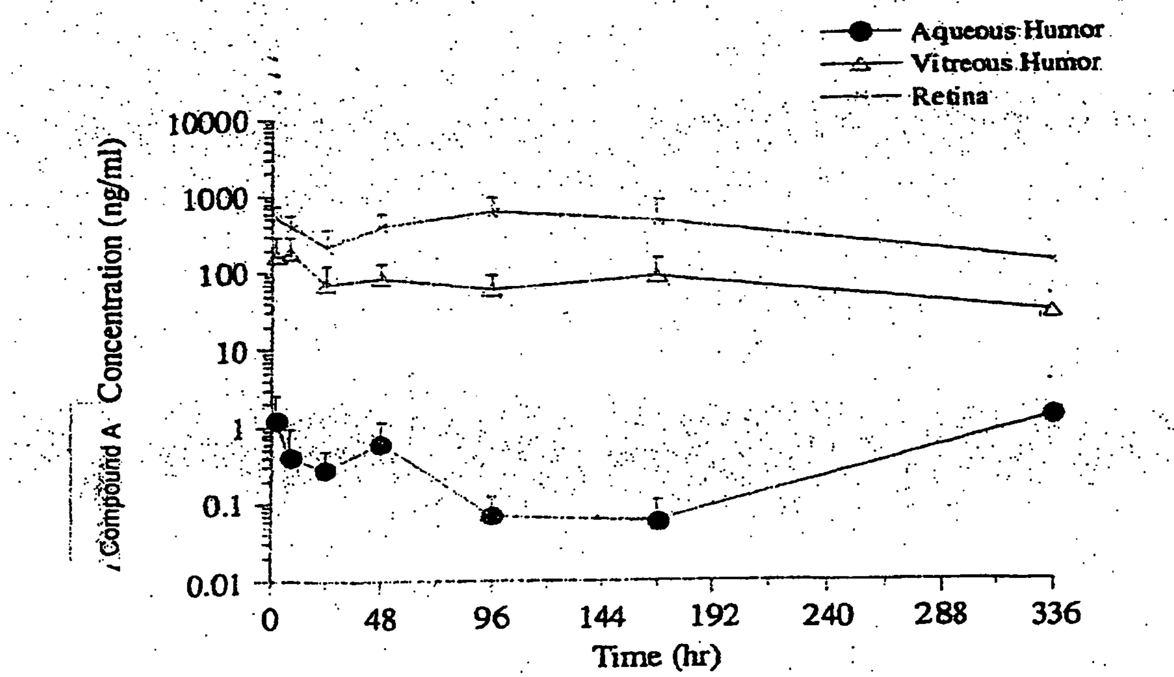

Aqueous Humor
Vitreous Humor
Retina
Compound A Concentration (ng/ml)
10000
1000
100
10
1
0.1
0.01
0
48
96
144
192
240
288
336
Time (hr)

Fig. 5

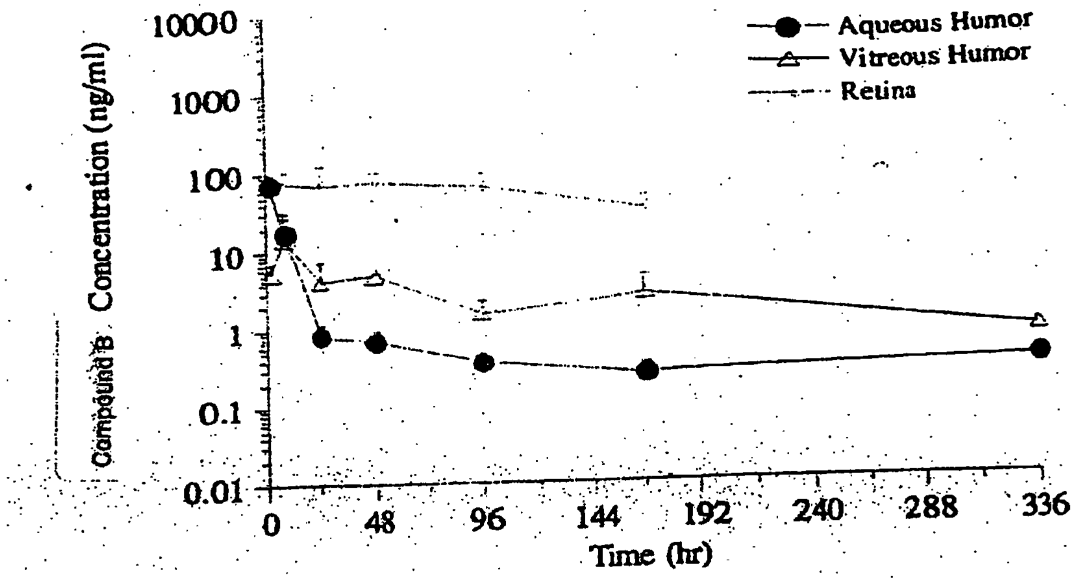

Aqueous Humor
Vitreous Humor
Retina
Compound B Concentration (ng/ml)
10000
1000
100
10
1
0.1
0.01
0
48
96
144
192
240
288
336
Time (hr)

Fig. 6

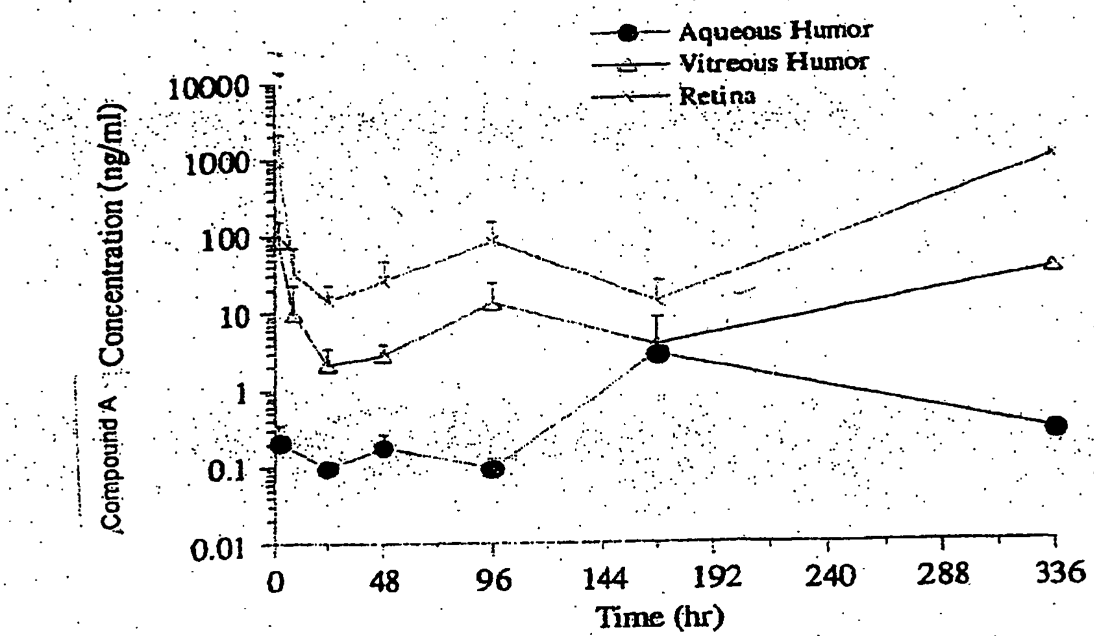

Aqueous Humor
Vitreous Humor
Retina
Compound A Concentration (ng/ml)
10000
1000
100
10
1
0.1
0.01
0
48
96
144
192
240
288
336
Time (hr)

Fig. 7

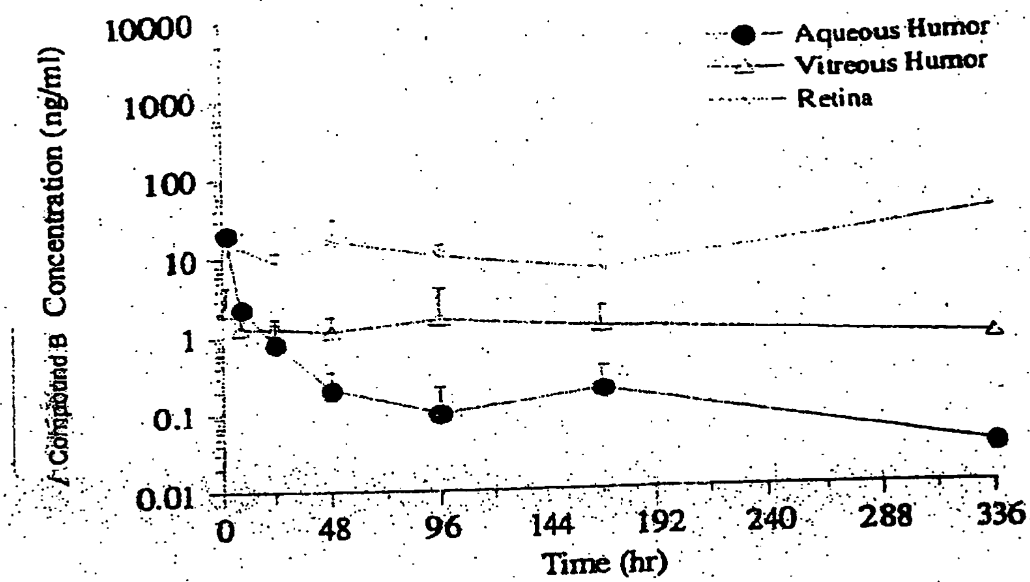

Aqueous Humor
Vitreous Humor
Retina
Compound B Concentration (ng/ml)
10000
1000
100
10
1
0.1
0.01
0
48
96
144
192
240
288
336
Time (hr)

Fig. 8

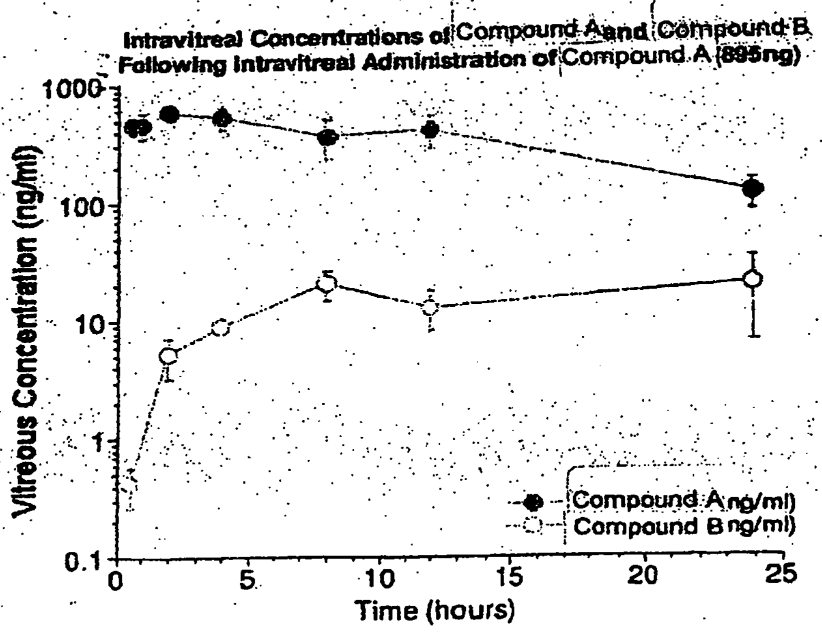

Intravitreal Concentrations of Compound A and Compound B
Following Intravitreal Administration of Compound A (895ng)
Vitreous Concentration (ng/ml)
1000
100
10
1
0.1
0
5
10
15
20
25
Time (hours)
Compound A ng/ml)
Compound B ng/ml)

Fig. 9

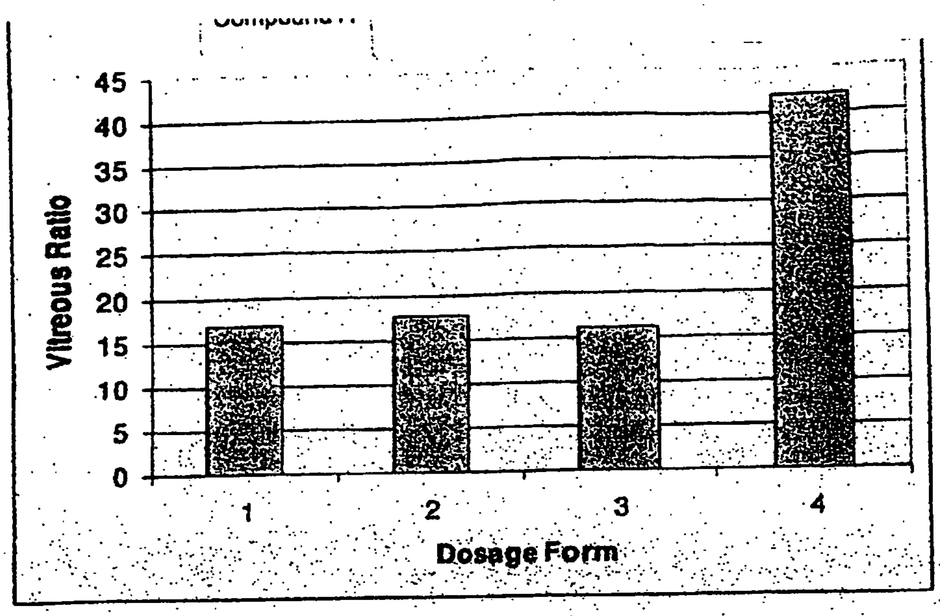

Vitreous Ratio
45
40
35
30
25
20
15
10
5
0
1
2
3
4
Dosage Form

Fig. 10

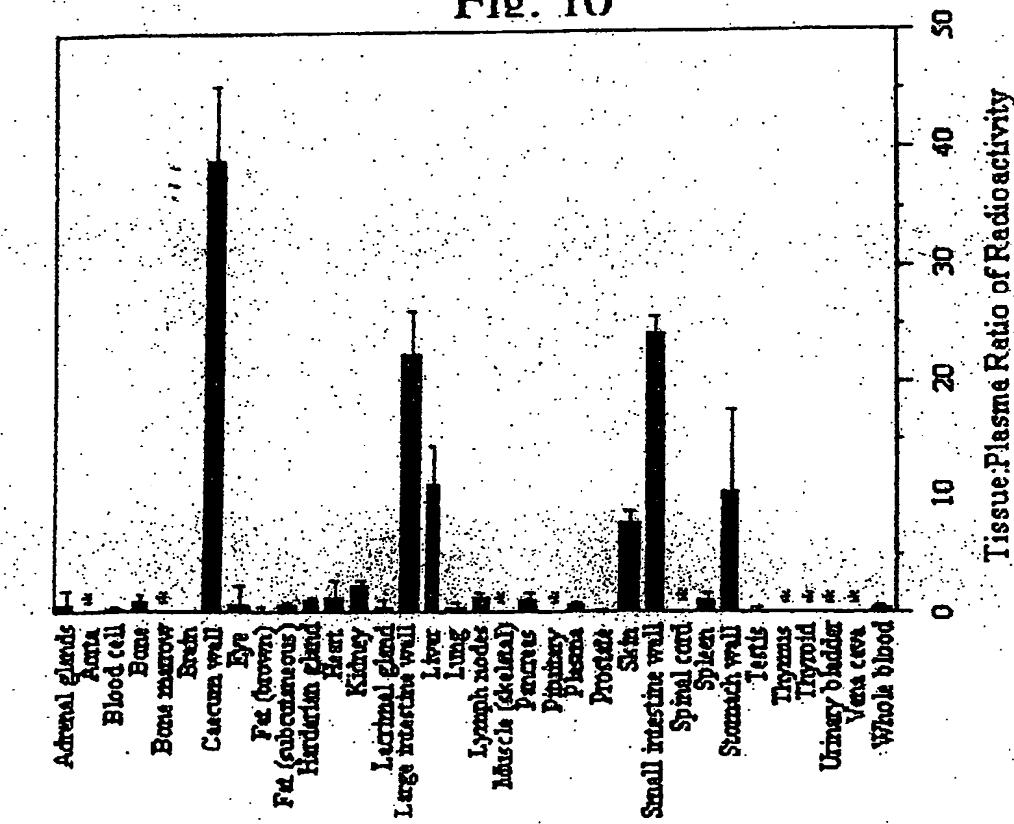

Tissue:Plasma Ratio of Radioactivity
0
10
20
30
40
50
Adrenal glands
Aorta
Blood cell
Bone
Bone marrow
Brain
Caecum wall
Eye
Fat (brown)
Fat (subcutaneous)
Harderian gland
Heart
Kidney
Lacrimal gland
Large intestine wall
Liver
Lung
Lymph nodes
Muscle (skeletal)
Pancreas
Pituitary
Plasma
Prostate
Skin
Small intestine wall
Spinal cord
Spleen
Stomach wall
Testis
Thymus
Thyroid
Urinary bladder
Vena cava
Whole blood

Fig. 11

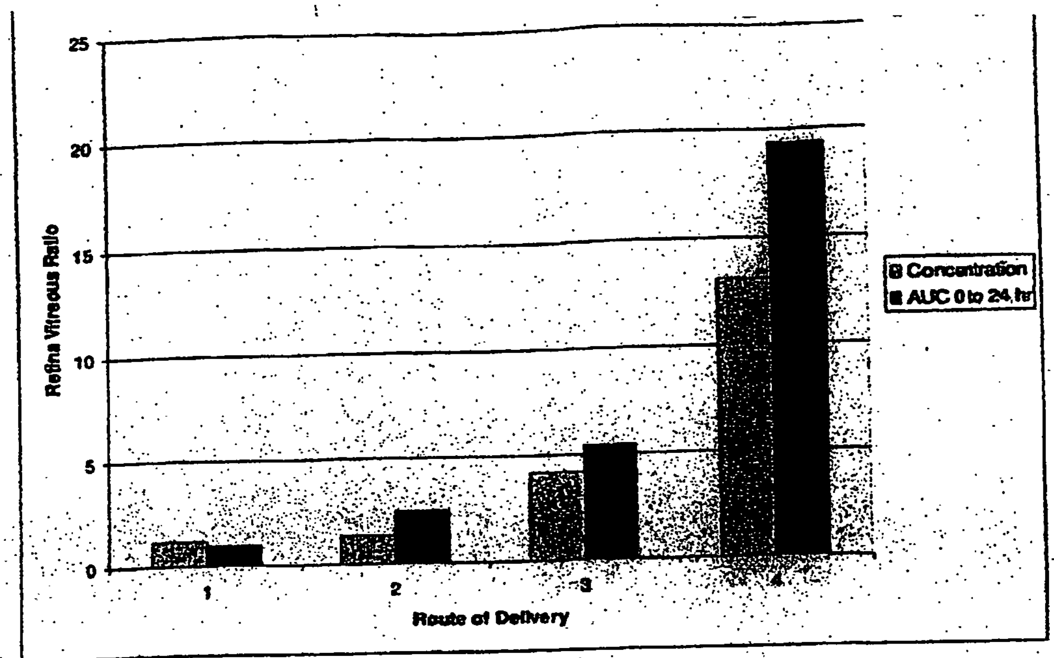


Fig. 12

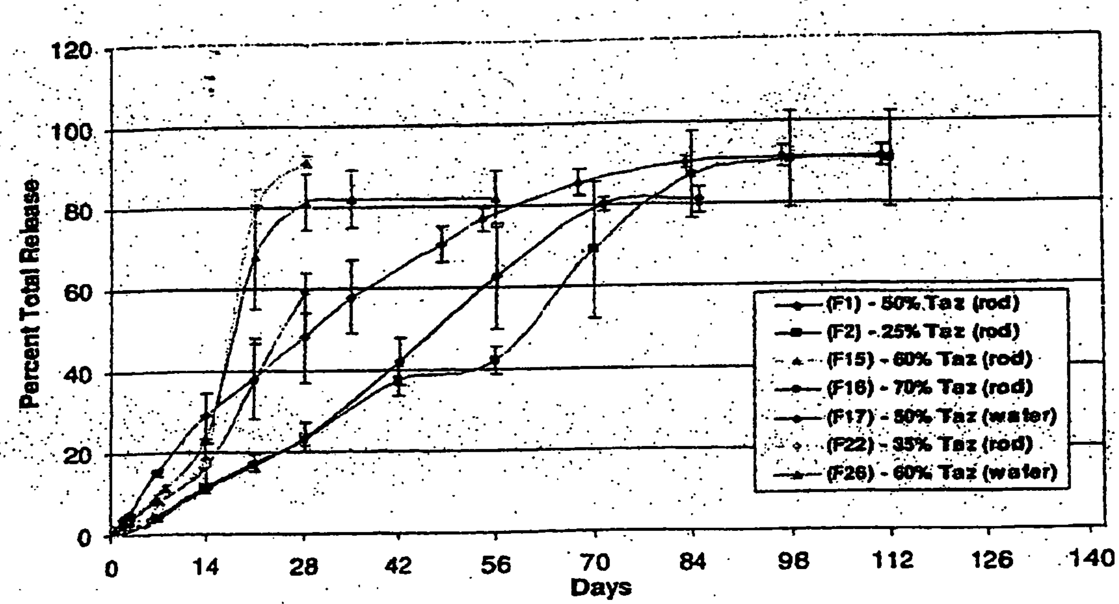
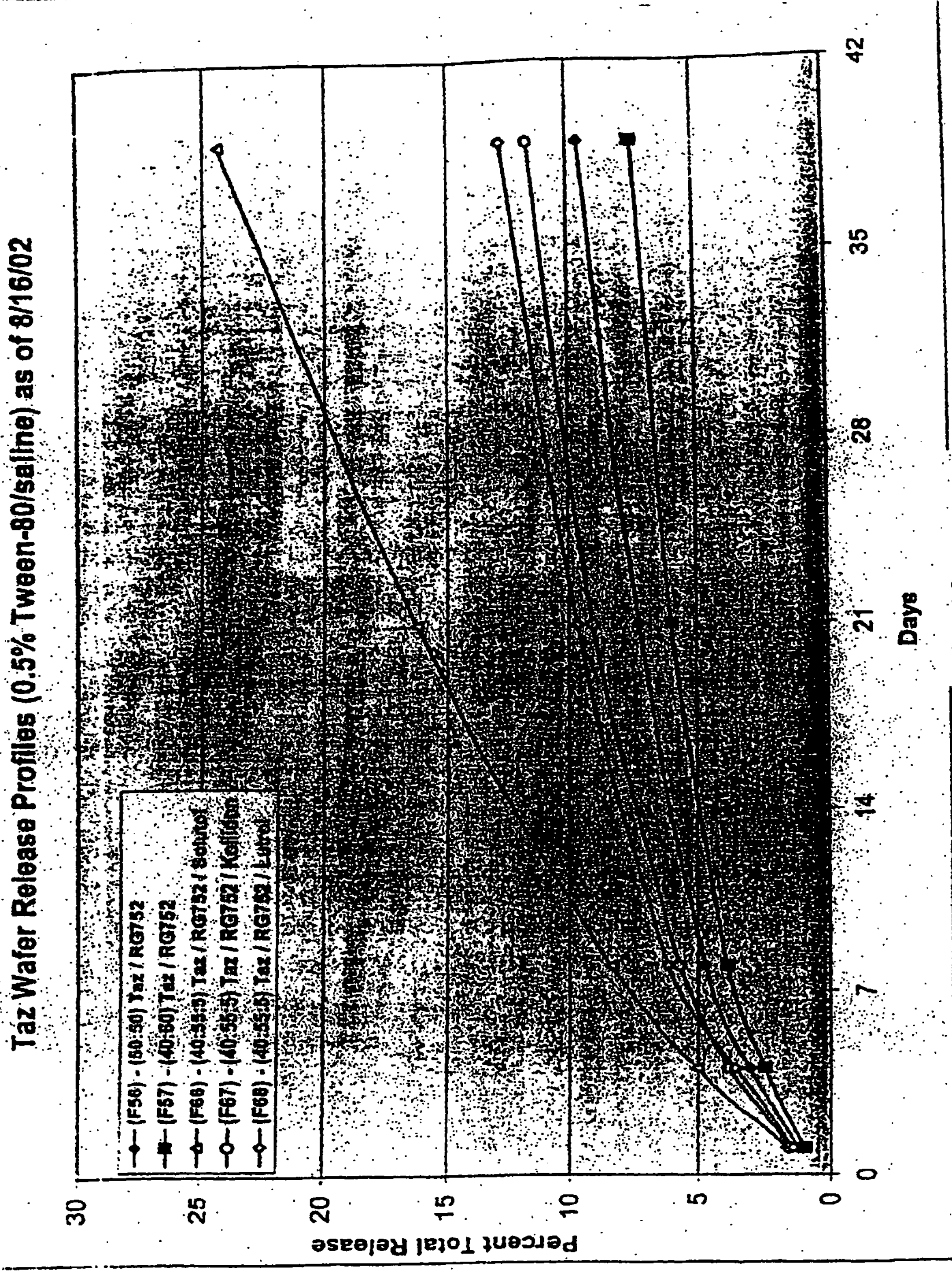
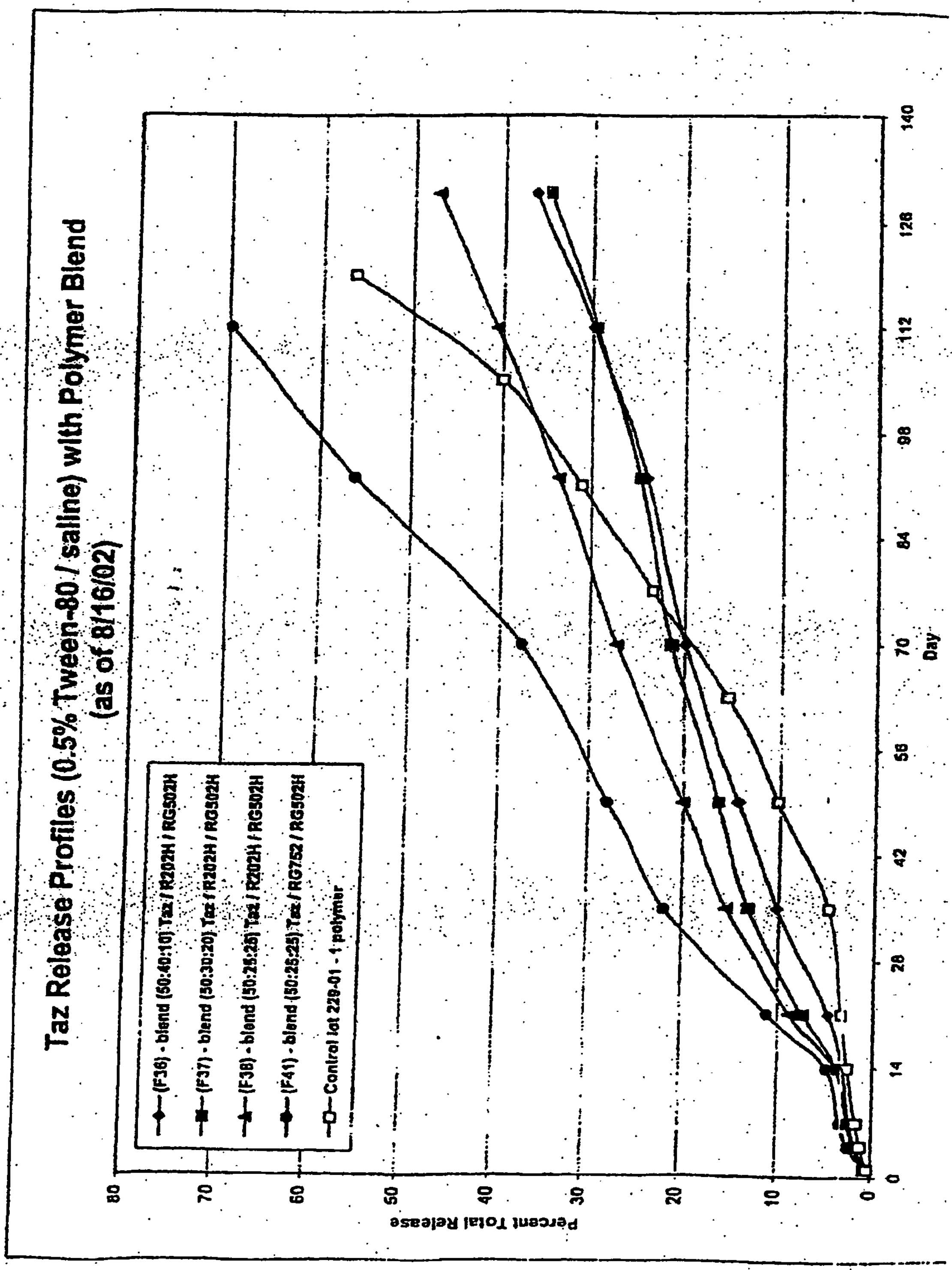


Fig. 15A


Taz Wafer Release Profiles (0.5% Tween-80/saline) as of 8/16/02
(F56) - (50:50) Taz / RG752
(F57) - (40:60) Taz / RG752
(F66) - (40:55:5) Taz / RG752 / Solutol
(F67) - (40:55:5) Taz / RG752 / Kolliphor
(F68) - (40:55:5) Taz / RG752 / Lutrol
Percent Total Release
30
25
20
15
10
5
0
0
7
14
21
28
35
42
Days


Taz Release Profiles (0.5% Tween-80 / saline) with Polymer Blend
(as of 8/16/02)
(F36) - blend (50:40:10) Taz / R202H / RG502H
(F37) - blend (50:30:20) Taz / R202H / RG502H
(F38) - blend (50:25:25) Taz / R202H / RG502H
(F41) - blend (50:25:25) Taz / RG752 / RG502H
Control lot 228-01 - 1 polymer
Percent Total Release
80
70
60
50
40
30
20
10
0
Day
0
14
28
42
56
70
84
98
112
126
140

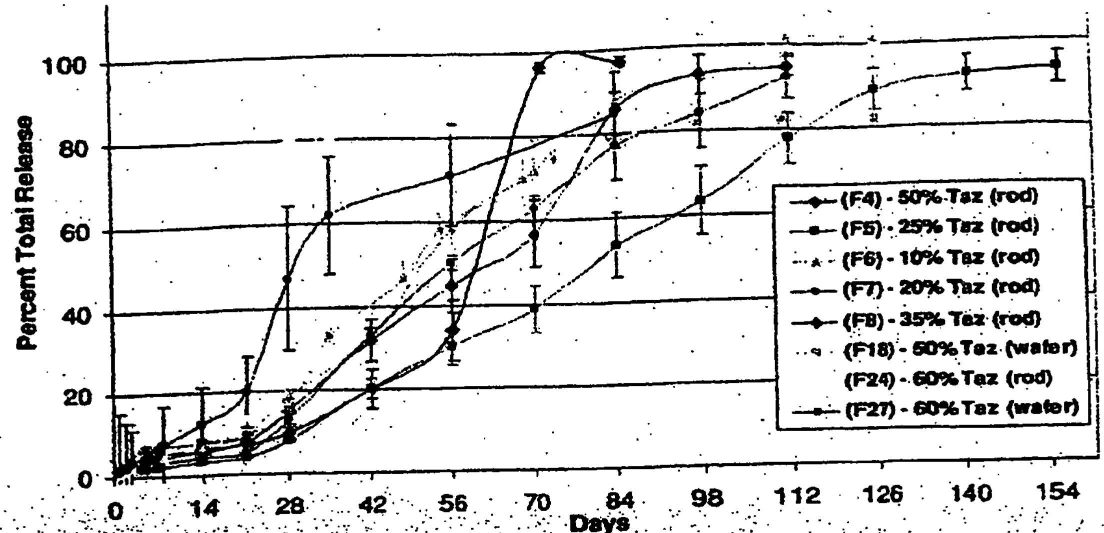


Fig. 15B

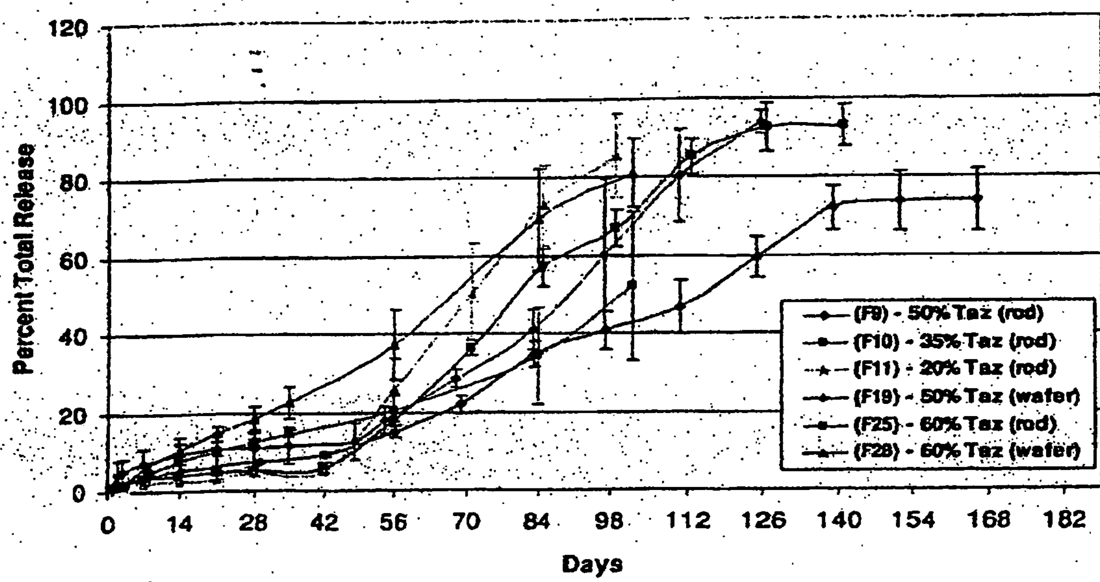


Fig. 15C

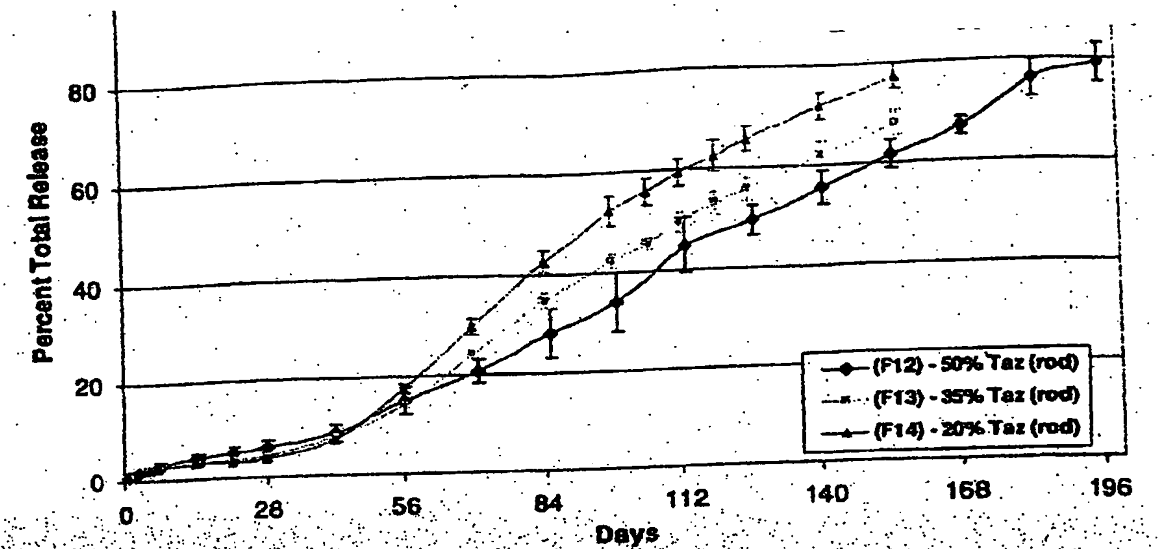


Fig. 15D

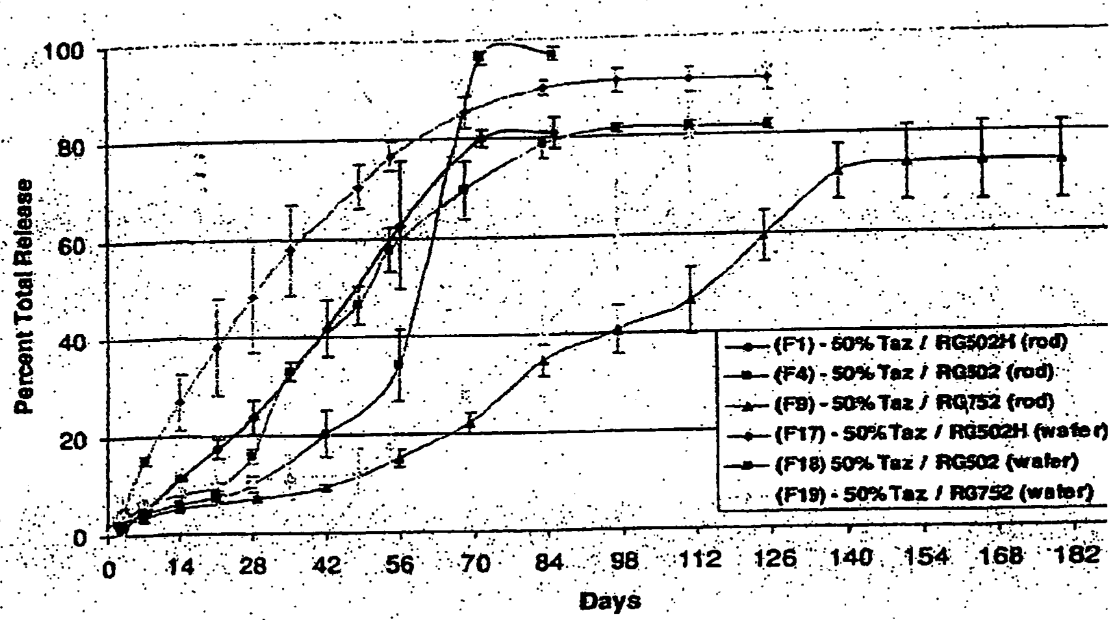


Fig. 16

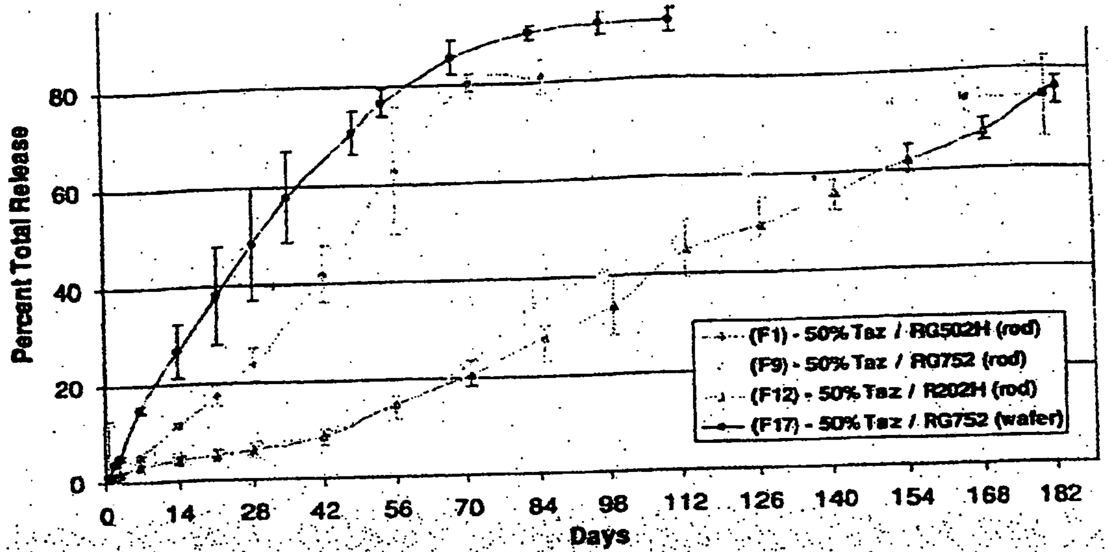

Percent Total Release
0
20
40
60
80
0
14
28
42
56
70
84
98
112
126
140
154
168
182
Days
(F1) - 50% Taz / RG502H (rod)
(F9) - 50% Taz / RG752 (rod)
(F12) - 50% Taz / R202H (rod)
(F17) - 50% Taz / RG752 (wafer)

Fig. 17

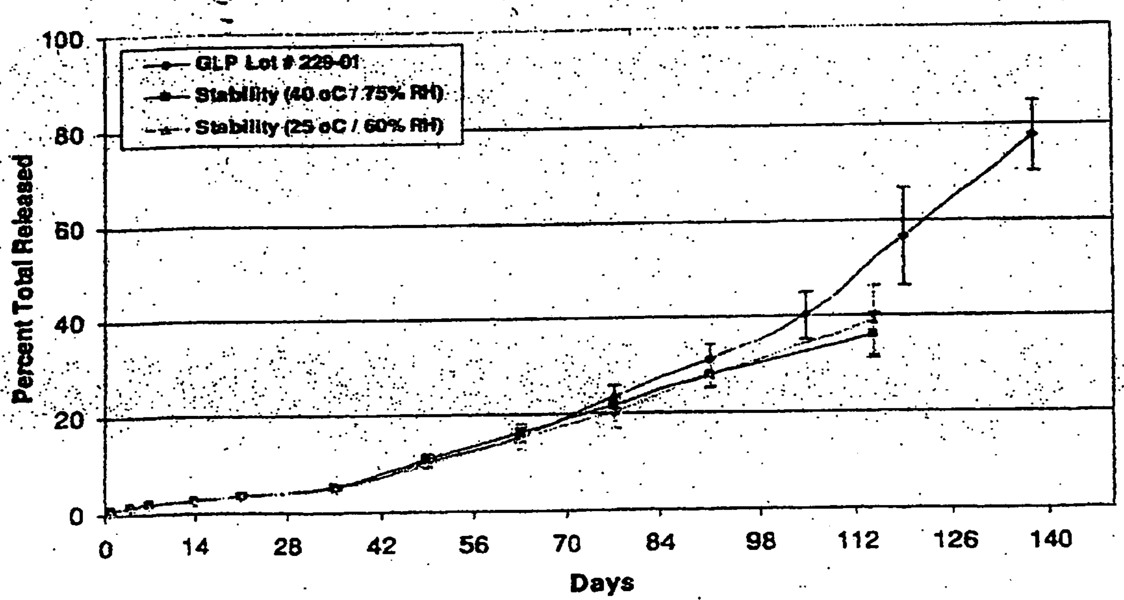

Percent Total Released
0
20
40
60
80
100
0
14
28
42
56
70
84
98
112
126
140
Days
GLP Lot # 229-01
Stability (40 oC / 75% RH)
Stability (25 oC / 60% RH)

Fig. 18

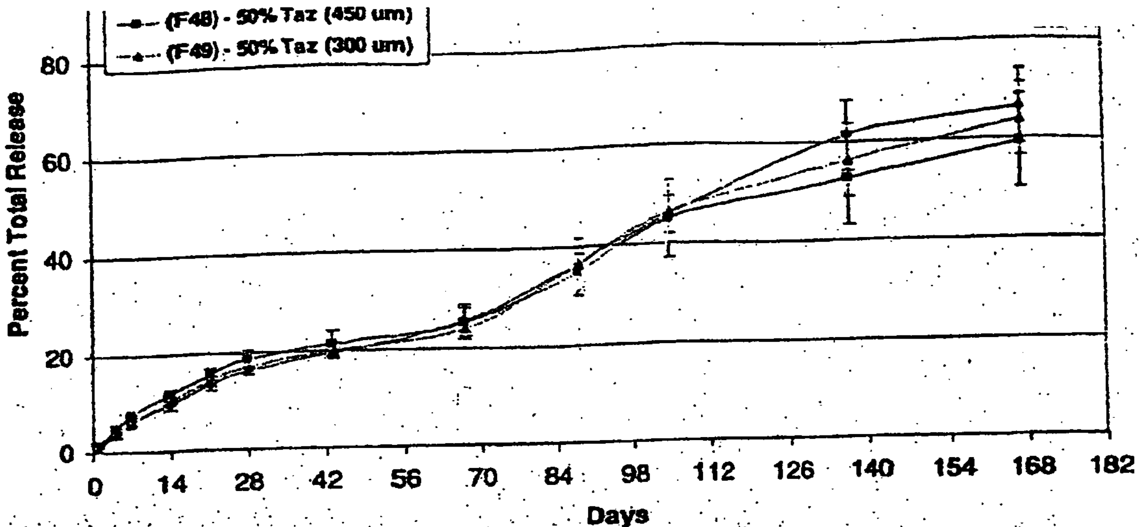

(F48) - 50% Taz (450 um)
(F49) - 50% Taz (300 um)
Percent Total Release
0
20
40
60
80
0
14
28
42
56
70
84
98
112
126
140
154
168
182
Days

Fig. 19

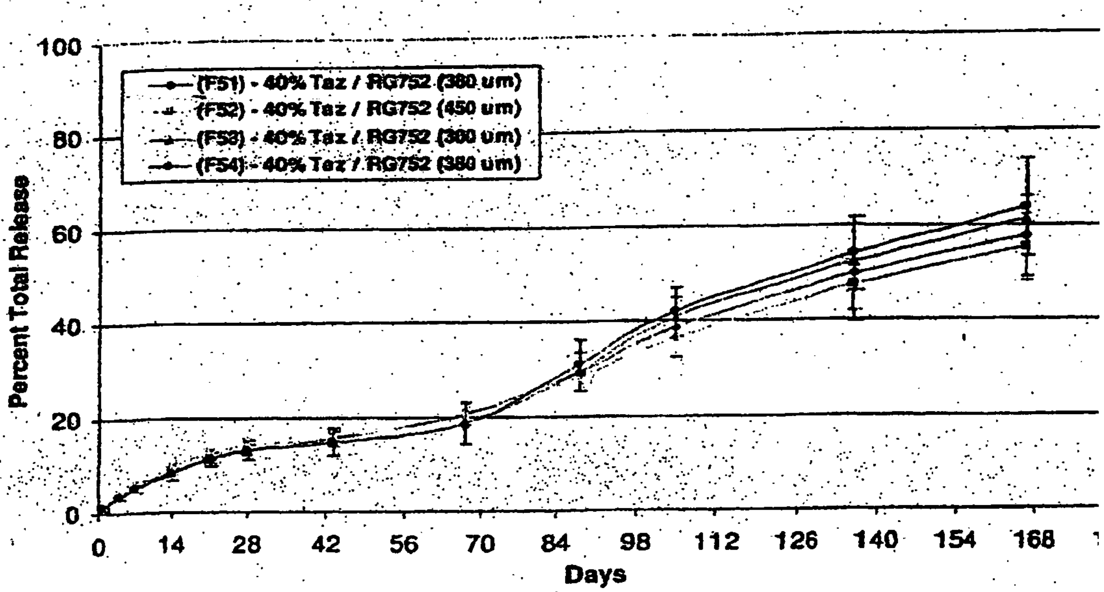

(F51) - 40% Taz / RG752 (380 um)
(F52) - 40% Taz / RG752 (450 um)
(F53) - 40% Taz / RG752 (380 um)
(F54) - 40% Taz / RG752 (380 um)
Percent Total Release
0
20
40
60
80
100
0
14
28
42
56
70
84
98
112
126
140
154
168
Days

Fig. 20

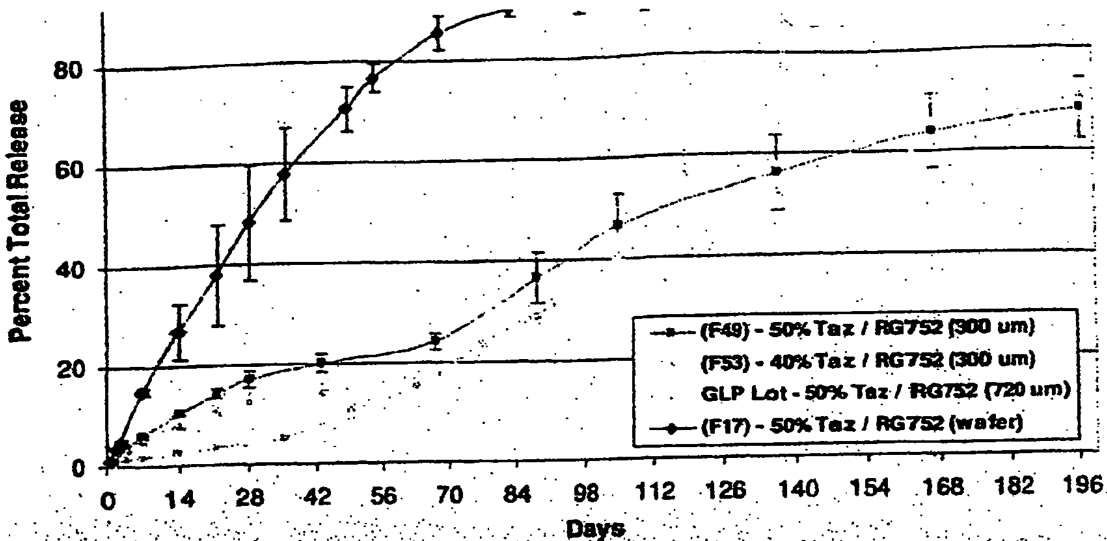

80
60
40
20
0
Percent Total Release
0 14 28 42 56 70 84 98 112 126 140 154 168 182 196
Days
(F49) - 50% Taz / RG752 (300 um)
(F53) - 40% Taz / RG752 (300 um)
GLP Lot - 50% Taz / RG752 (720 um)
(F17) - 50% Taz / RG752 (wafer)

Fig. 21

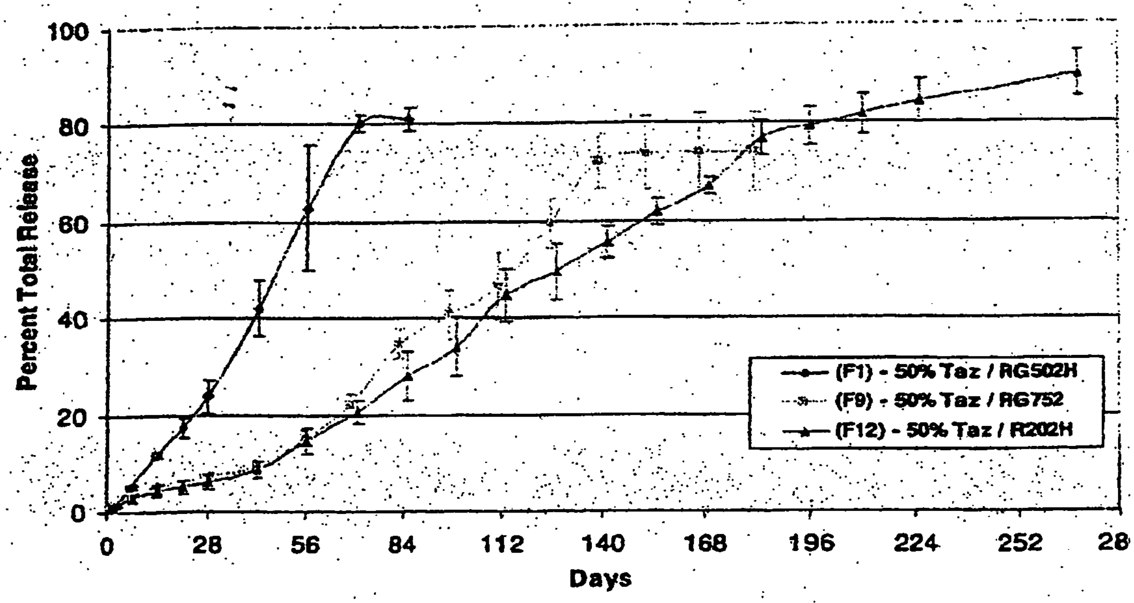

100
80
60
40
20
0
Percent Total Release
0 28 56 84 112 140 168 196 224 252 28
Days
(F1) - 50% Taz / RG502H
(F9) - 50% Taz / RG752
(F12) - 50% Taz / R202H

Fig. 22

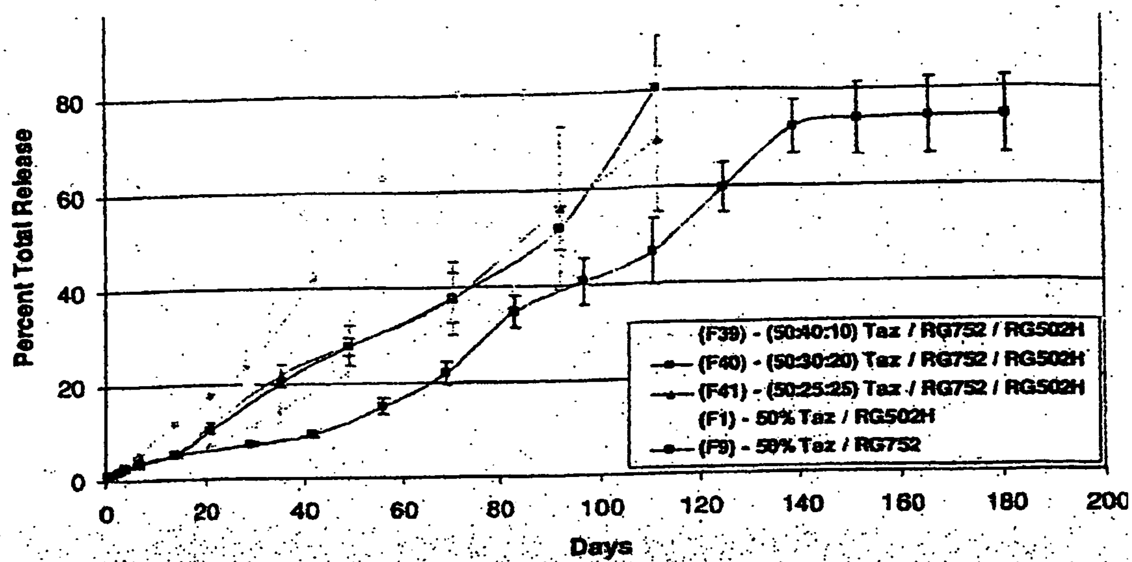


Fig. 23A

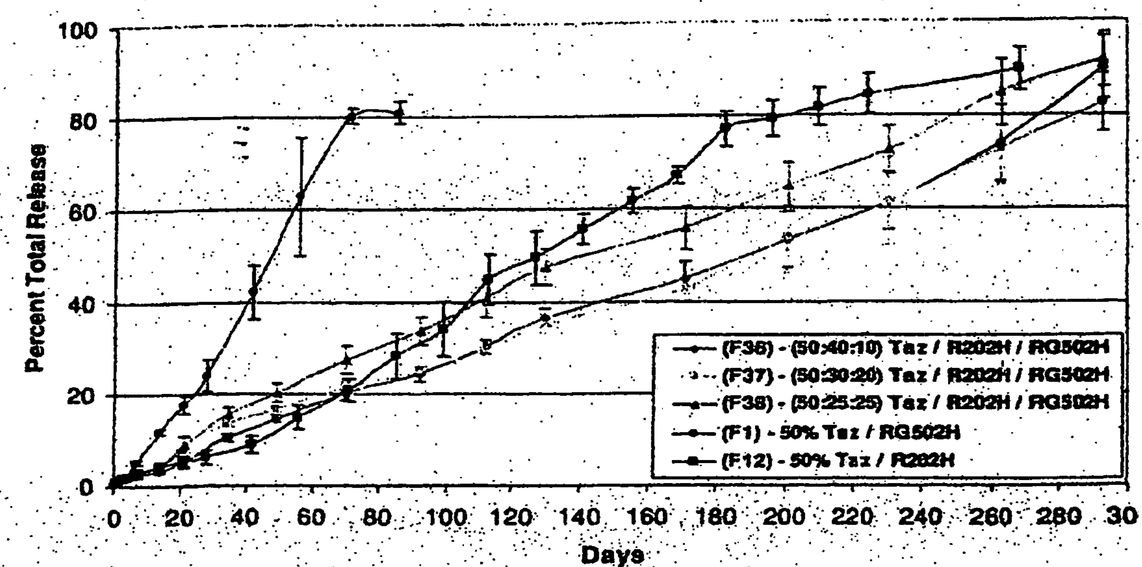


Fig. 23B

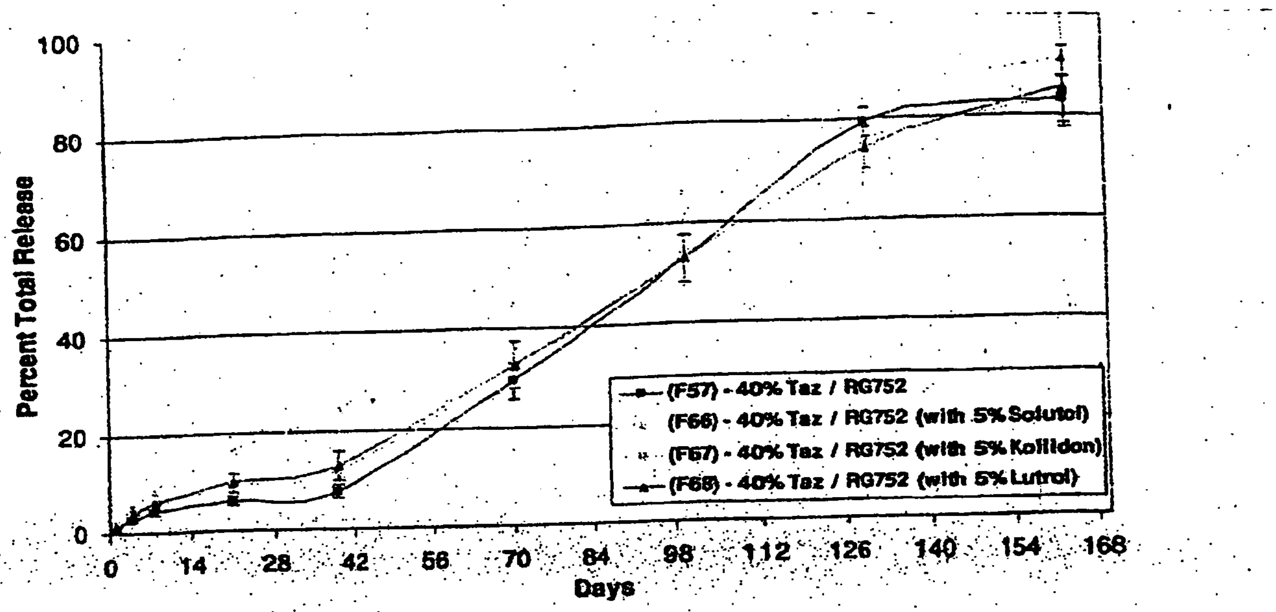

Percent Total Release
100
80
60
40
20
0
0 14 28 42 56 70 84 98 112 126 140 154 168
Days
(F57) - 40% Taz / RG752
(F66) - 40% Taz / RG752 (with 5% Solutol)
(F67) - 40% Taz / RG752 (with 5% Kollidon)
(F68) - 40% Taz / RG752 (with 5% Lutrol)

Fig. 24

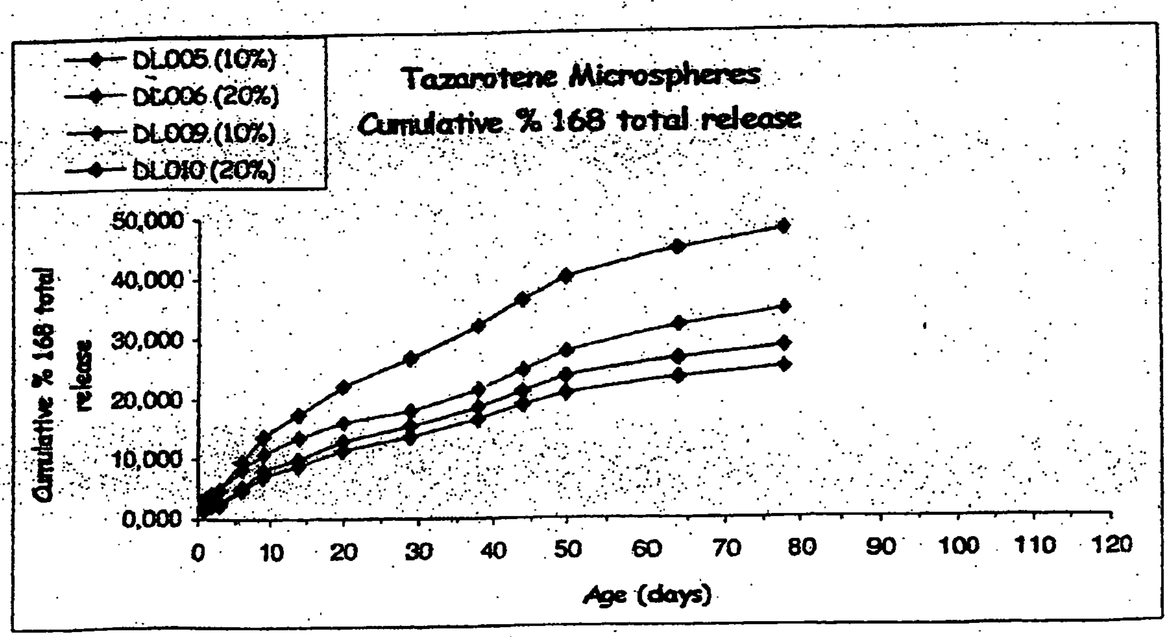
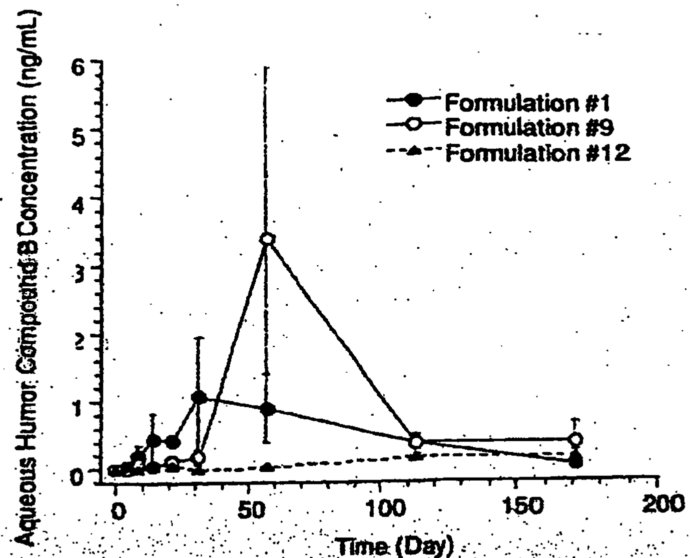

DL005 (10%)
DL006 (20%)
DL009 (10%)
DL010 (20%)
Tazarotene Microspheres
Cumulative % 168 total release
Cumulative % 168 total release
50,000
40,000
30,000
20,000
10,000
0,000
0 10 20 30 40 50 60 70 80 90 100 110 120
Age (days)

Fig. 25


Aqueous Humor Compound B Concentration (ng/mL)
Formulation #1
Formulation #9
Formulation #12
Time (Day)
0
1
2
3
4
5
6
50
100
150
200

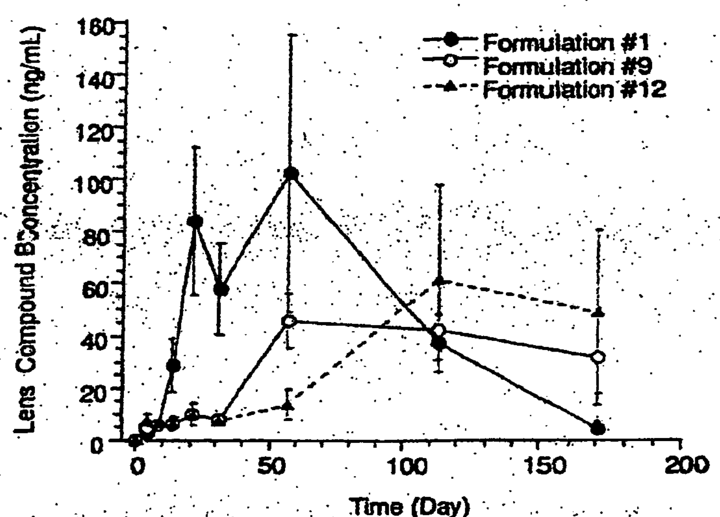

Lens Compound B Concentration (ng/mL)
Formulation #1
Formulation #9
Formulation #12
Time (Day)
0
20
40
60
80
100
120
140
160
50
100
150
200

FIG. 26

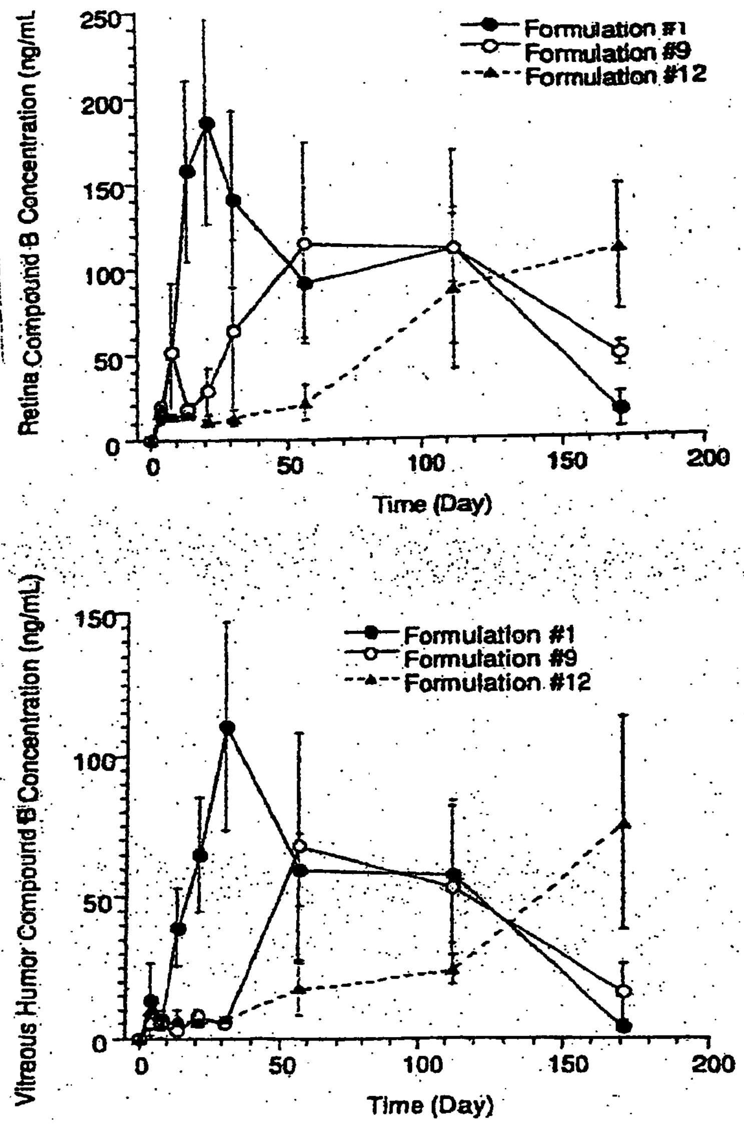

Formulation #1
Formulation #9
Formulation #12
Retina Compound B Concentration (ng/mL)
Time (Day)
0
50
100
150
200
250
Formulation #1
Formulation #9
Formulation #12
Vitreous Humor Compound B Concentration (ng/mL)
Time (Day)
0
50
100
150
200

Fig. 27

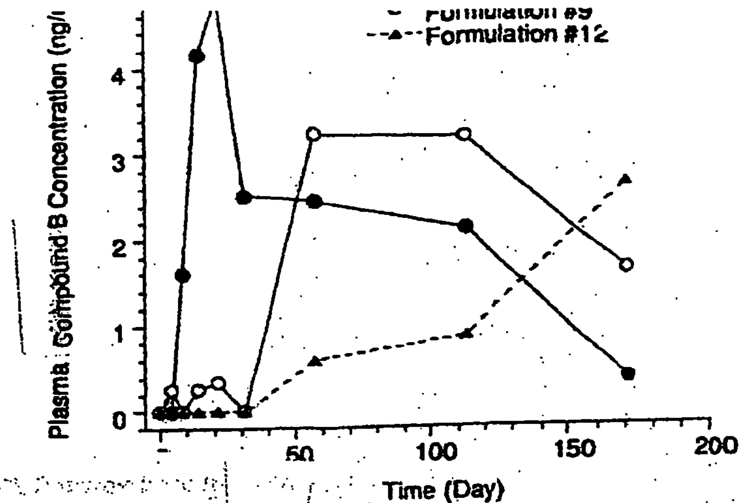

Formulation #12
Plasma Compound B Concentration (ng/
Time (Day)
0
1
2
3
4
50
100
150
200

Fig. 28

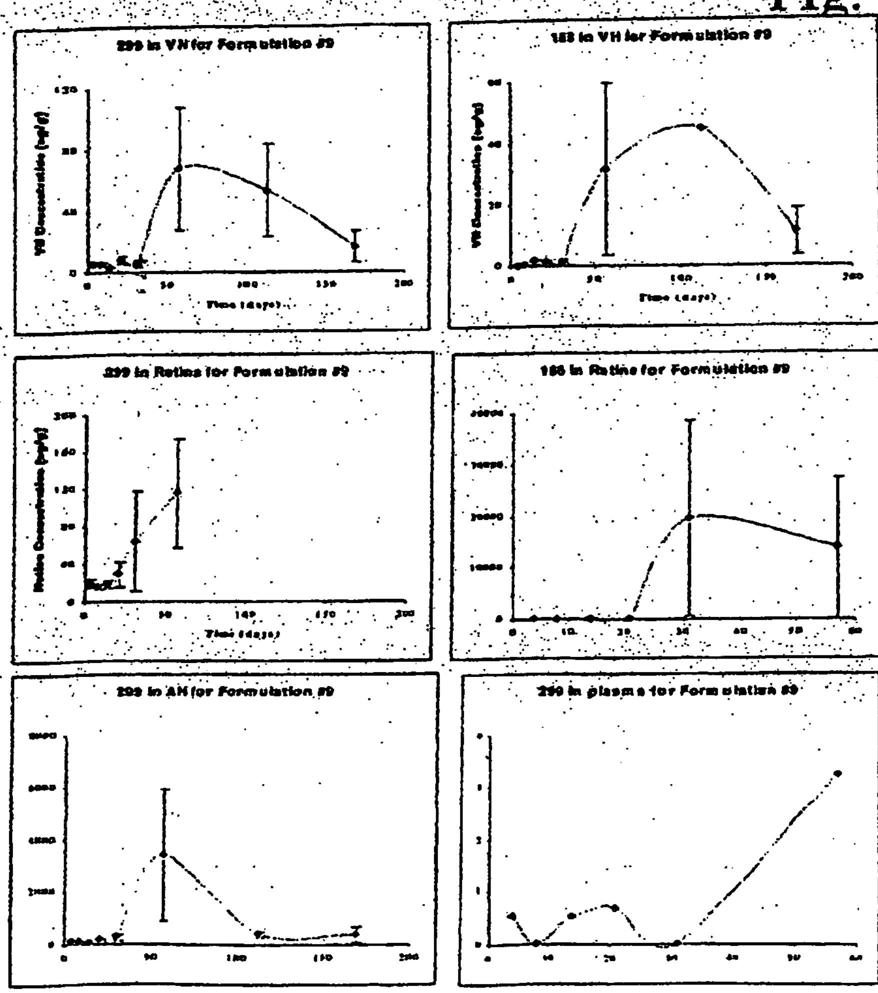


Fig. 29

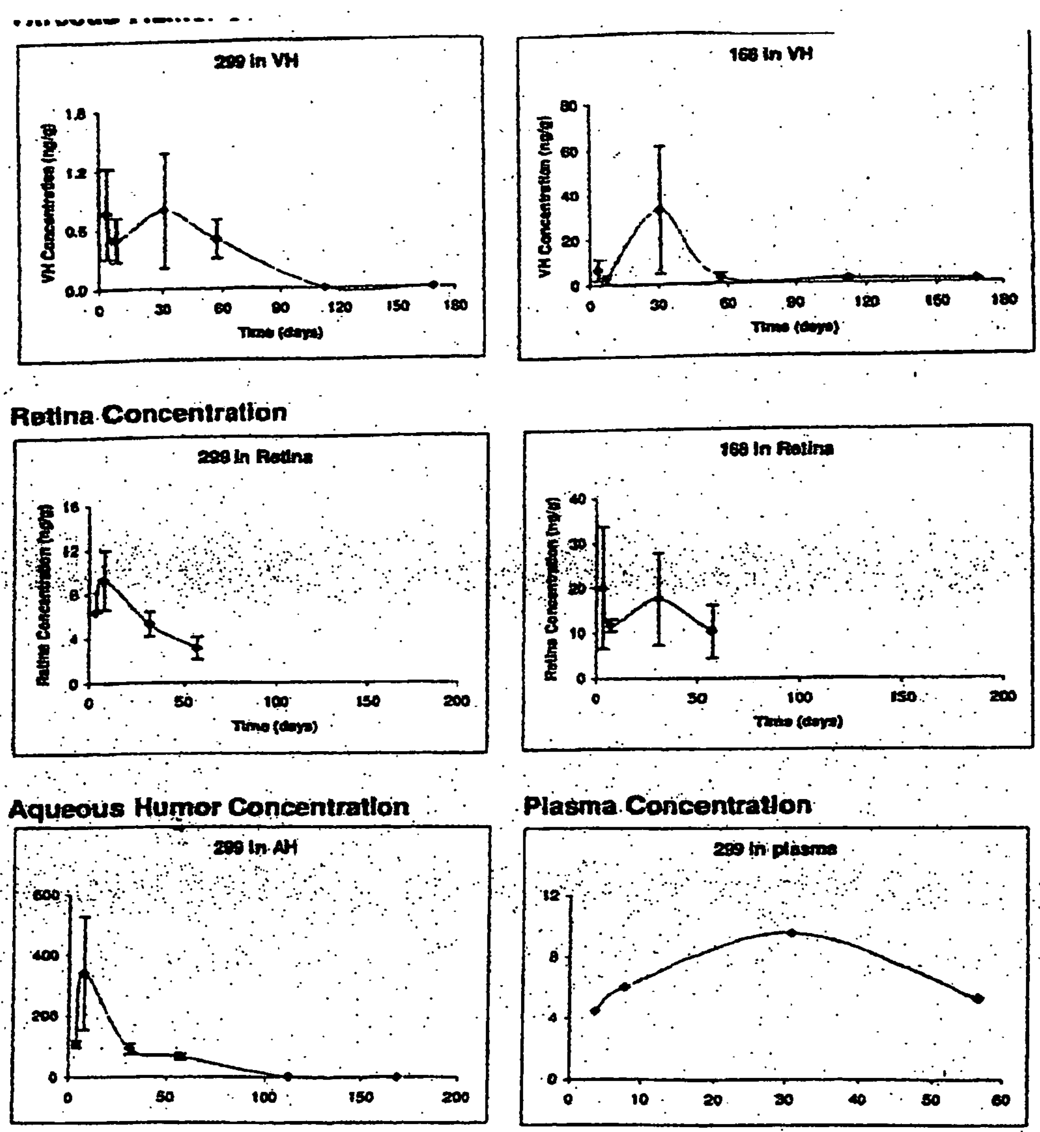

299 in VH
VH Concentration (ng/g)
Time (days)
168 in VH
VH Concentration (ng/g)
Time (days)
Retina Concentration
299 in Retina
Retina Concentration (ng/g)
Time (days)
168 in Retina
Retina Concentration (ng/g)
Time (days)
Aqueous Humor Concentration
299 in AH
Plasma Concentration
299 in plasma

Fig. 30

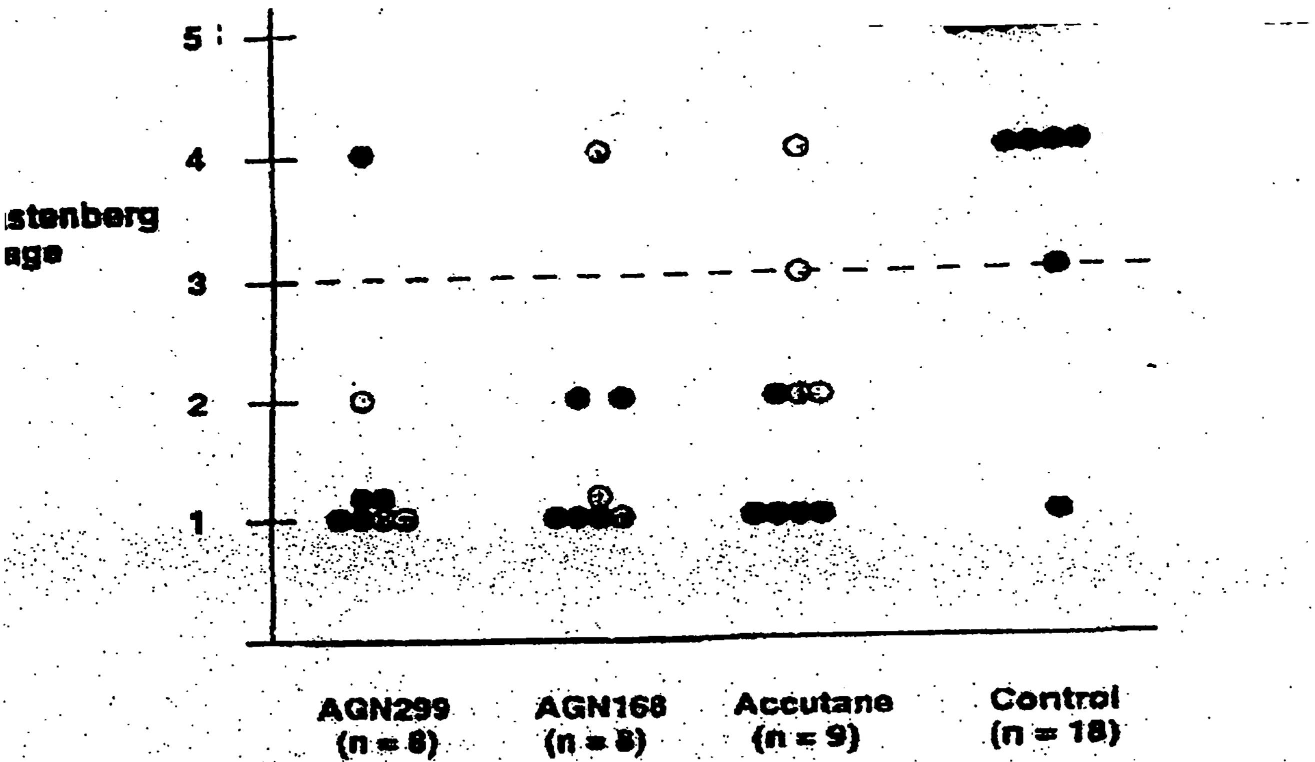

stenberg
age
5
4
3
2
1
AGN299
(n = 8)
AGN168
(n = 8)
Accutane
(n = 9)
Control
(n = 18)

Fig. 31

Figure 32: Visual aspect after drying

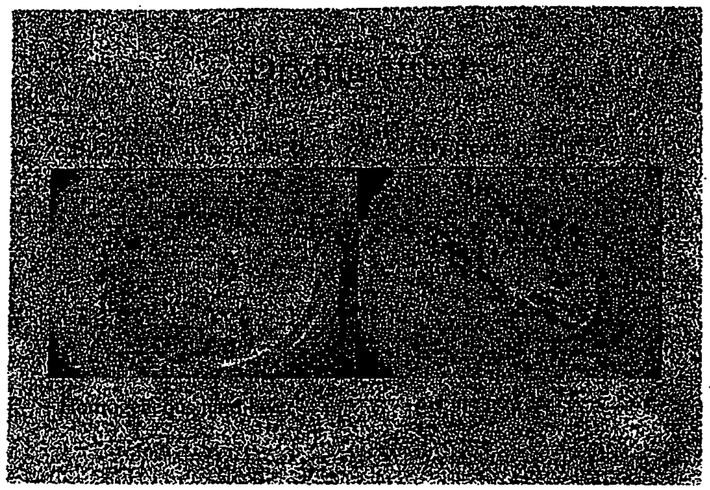


Figure 33: Effect of gamma sterilization

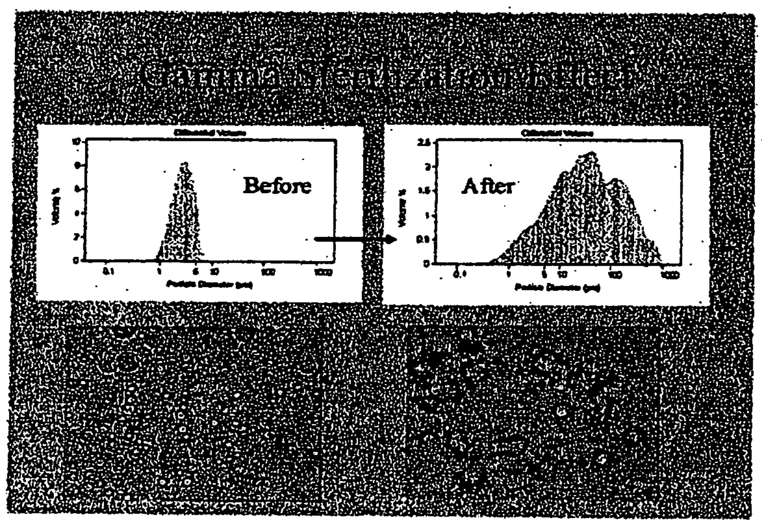
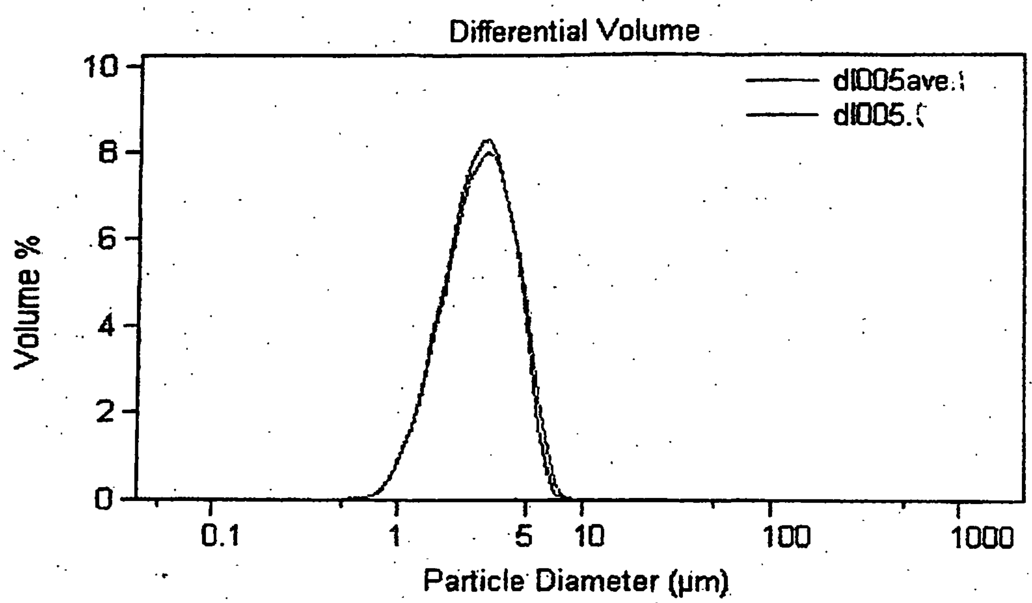


Figure 34: Overlay of non sterile and sterile Microspheres using cold pack



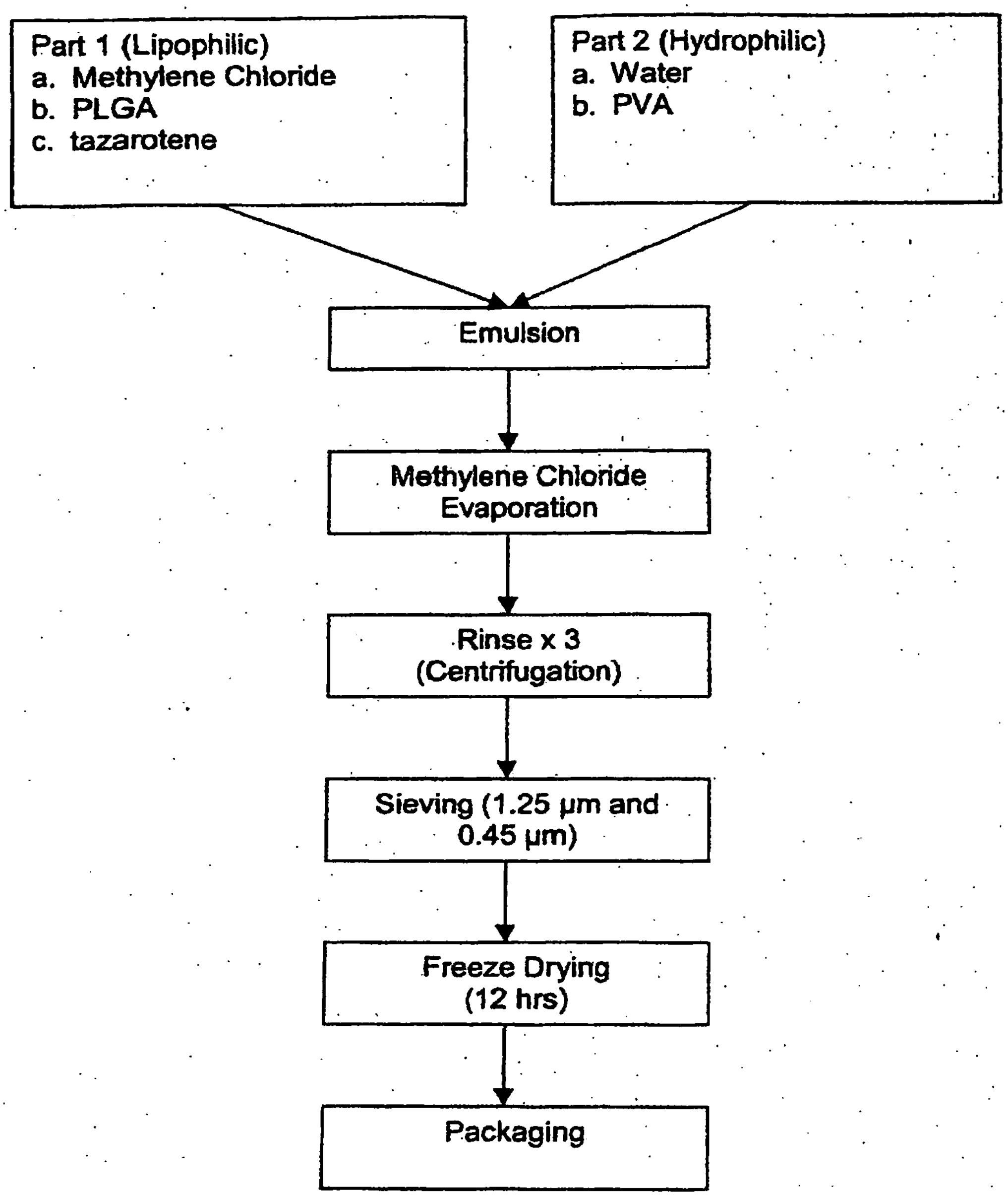

Part 1 (Lipophilic)
a. Methylene Chloride
b. PLGA
c. tazarotene
Part 2 (Hydrophilic)
a. Water
b. PVA
Emulsion
Methylene Chloride Evaporation
Rinse x 3 (Centrifugation)
Sieving (1.25 μm and 0.45 μm)
Freeze Drying (12 hrs)
Packaging

FIG. 35

Figure 36: Typical microscopic appearance

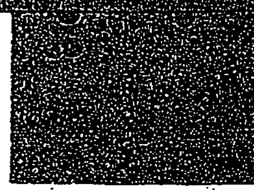
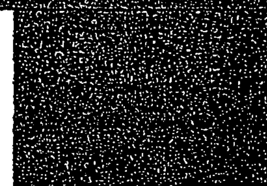
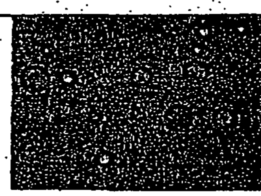
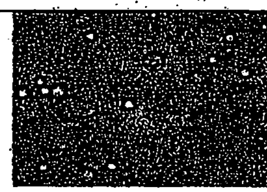
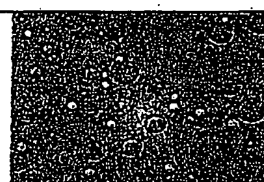
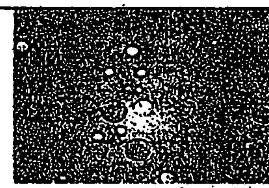
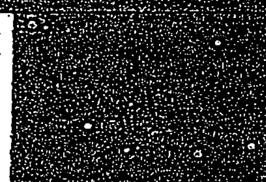
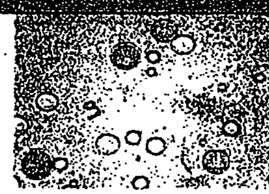
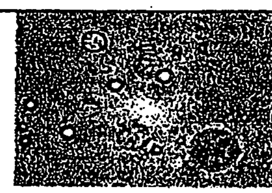
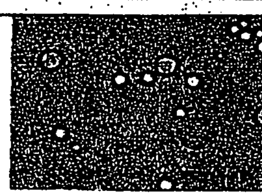
Batch #	Non sterile	Sterile
DL 005 (10%)		
DL 006 (20%)		
DL 007 (Placebo)		
DL 009 (10%)		
DL 010 (20%)		
DL 008 (Placebo)		

Figure 37: Dissolution profile trends

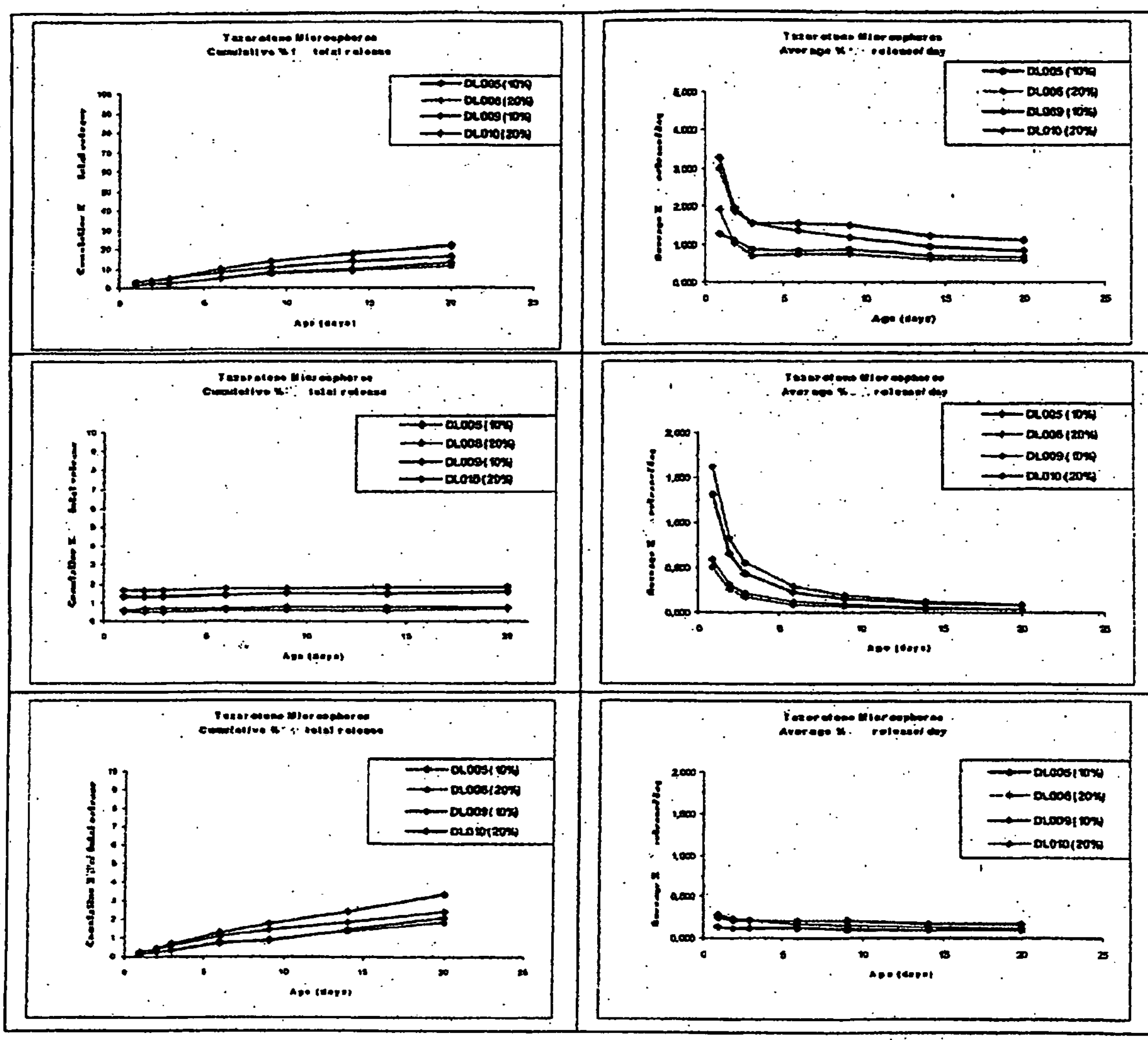


Figure 38: Microscopic appearance at 40°C, magnification 20, 60 and 100

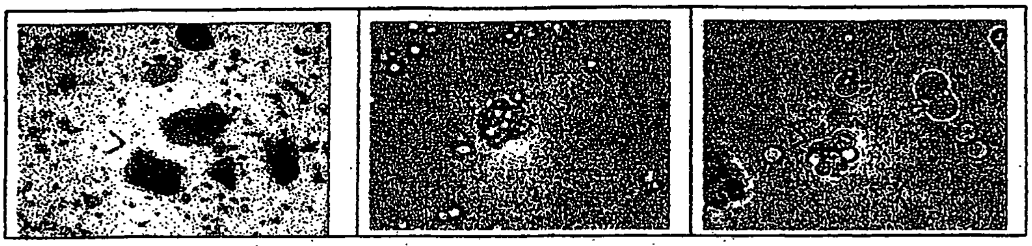


Figure 39: Irregular shape

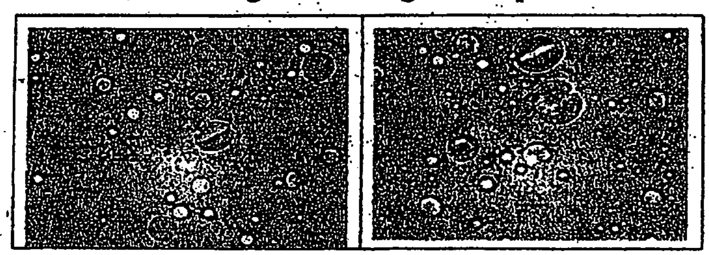
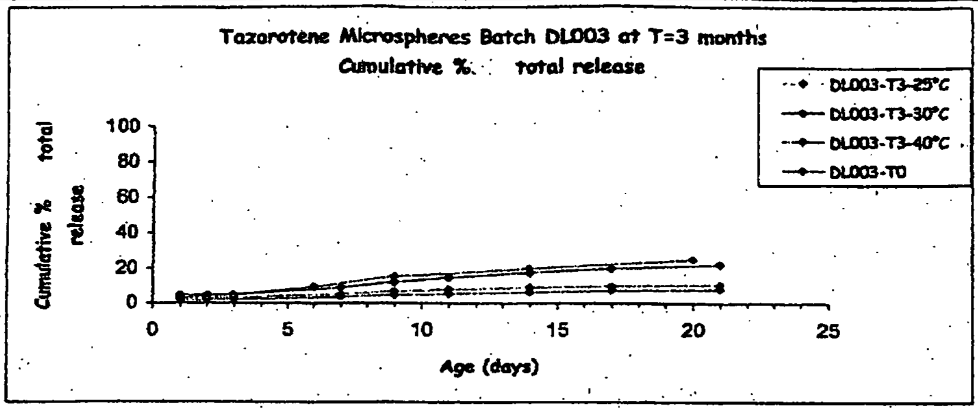


Figure 40: Dissolution profile trends for Batch DL003



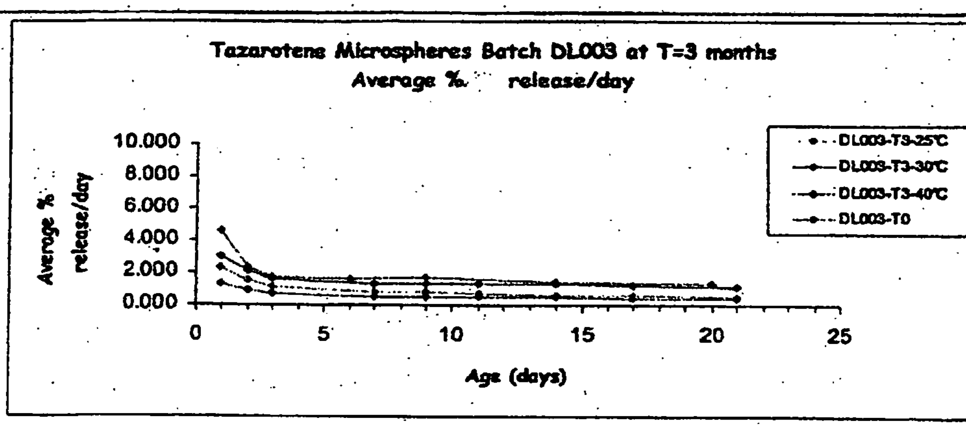


Figure 41: Dissolution profile trends for Batches DL005, DL006, DL009 and DL010

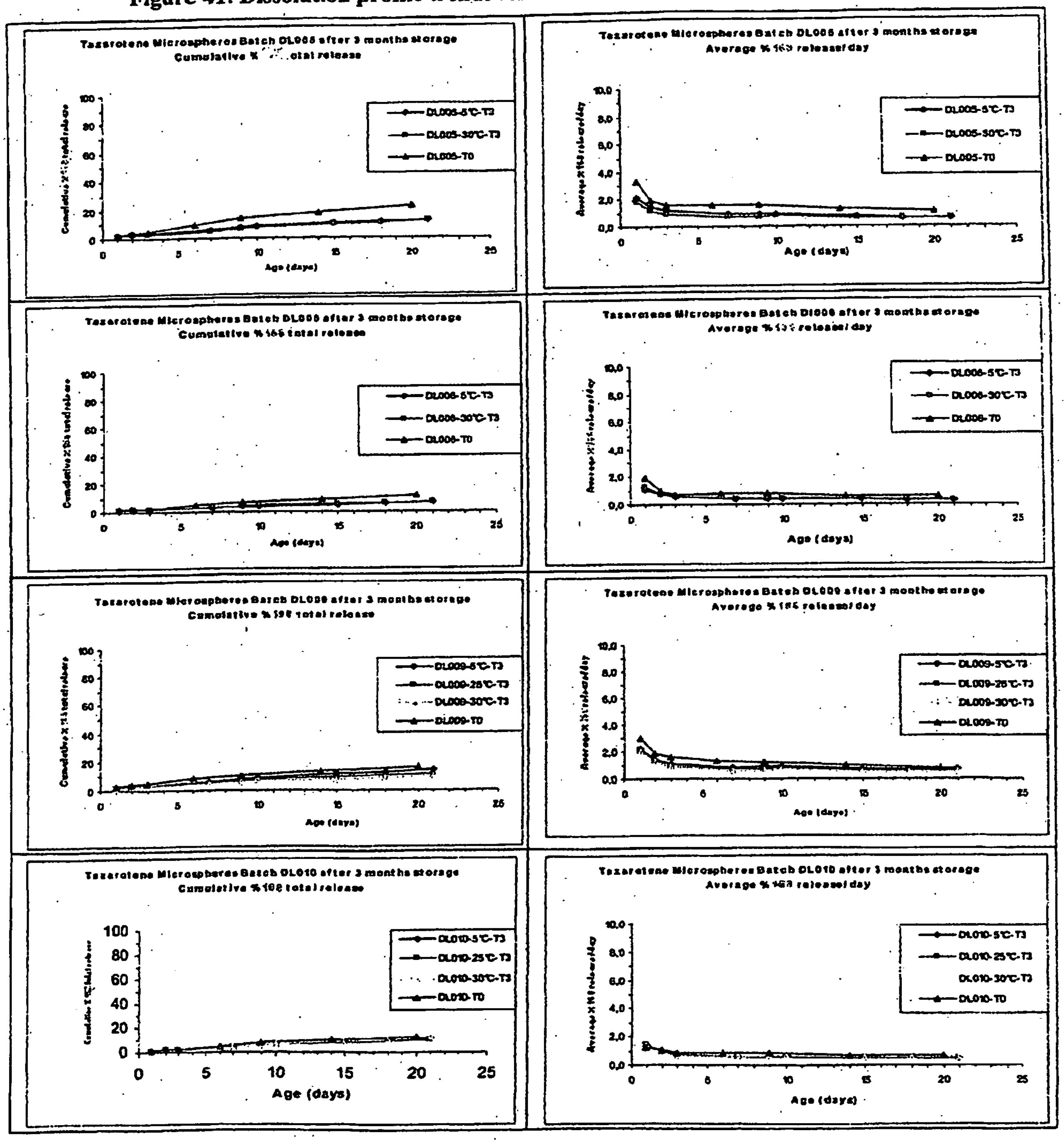


Figure 42: 44 days dissolution profile for batch DL003

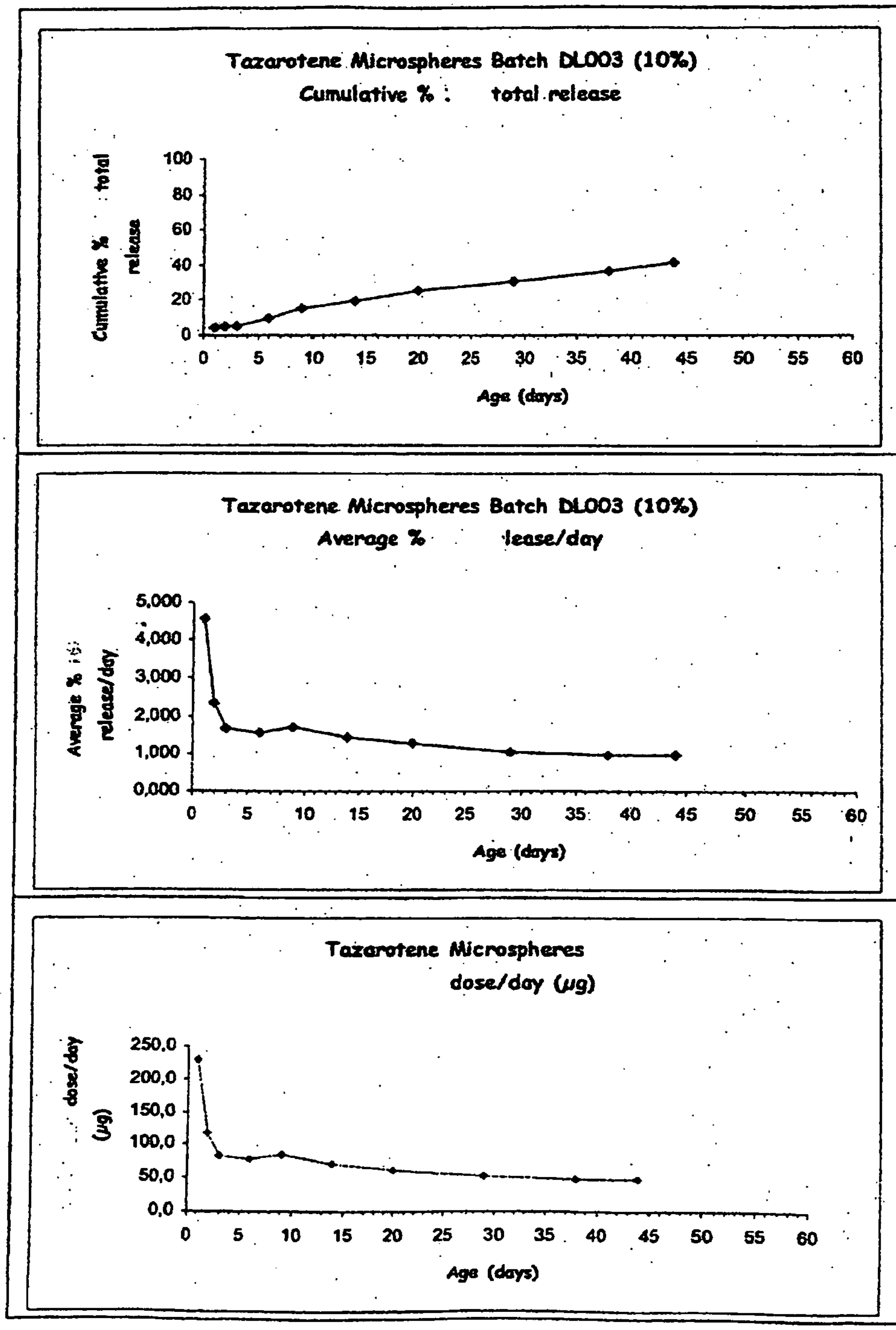


Figure 43: 252 days dissolution profile for batches DL005, DL006, DL009 and DL010

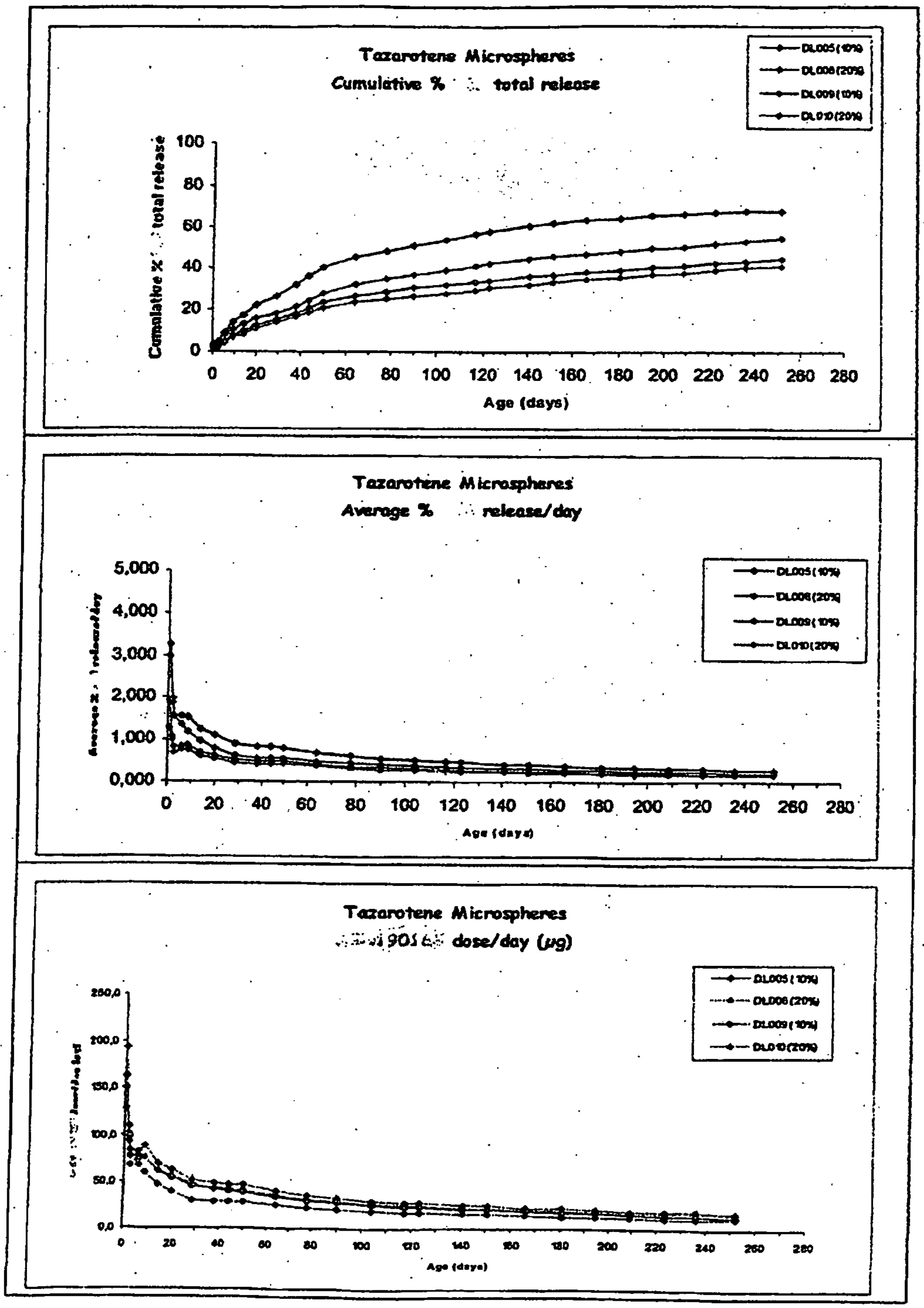


Figure 44: 10% versus 20% Tazarotene microspheres

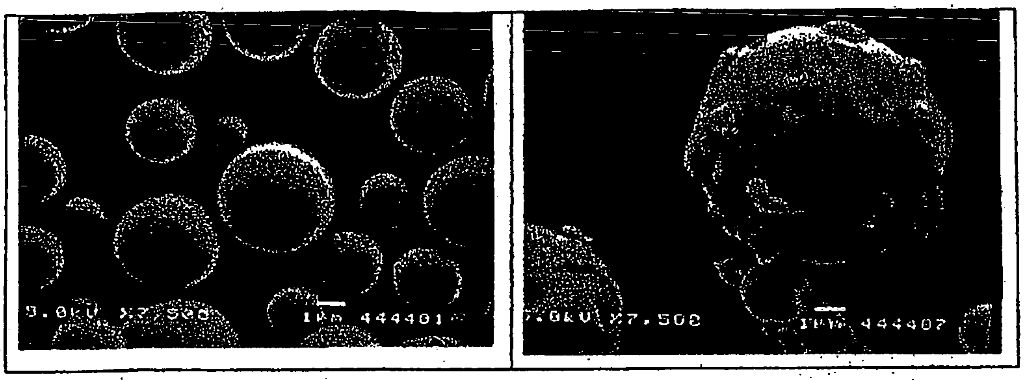


Figure 45: Gamma sterilization effect (non sterile/sterile 10% microspheres)

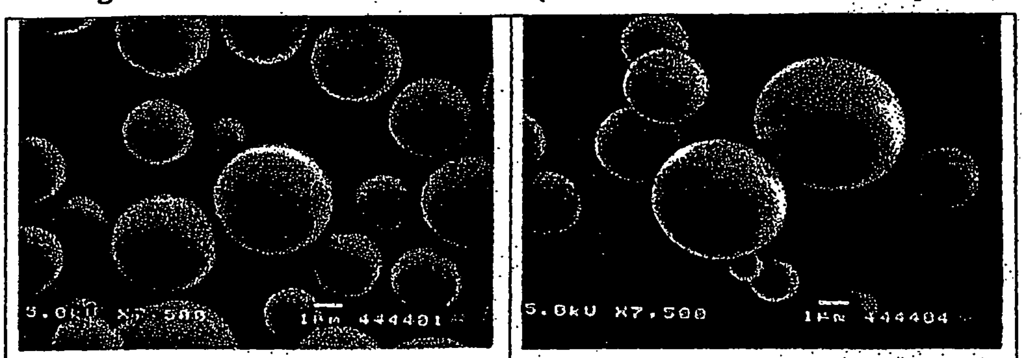


Figure 46: Aspect of microspheres after dissolution (21 days/45 days)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/015018

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/16 A61K31/07 A61K31/203

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 110 485 A (OLEJNIK ET AL) 29 August 2000 (2000-08-29) claims 1-9 column 4, line 21 - column 5, line 13 column 6, line 1 - column 7, line 13	1-10,12, 14-28
X	US 6 001 386 A (ASHTON ET AL) 14 December 1999 (1999-12-14) claims 1-18 column 5, line 30 - column 8, line 15 examples 2,3	1,2,5-7, 10,14, 22-27
X	US 2002/022047 A1 (OLEJNIK OREST ET AL) 21 February 2002 (2002-02-21) paragraphs '0039!, '0046!, '0062! - '0067! claims 1-24	1-10,12, 14-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 September 2005	04/10/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schifferer, H

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KIV LO-M. SIREN-V. ITT-C-R. IMMONEN-I.: "Biodegradable tube implants in experimental glaucoma surgery in the rabbit." JOURNAL OF MATERIALS SCIENCE: MATERIALS IN MEDICINE, vol. 10, 1999, pages 53-58, XP009054235 page 53, right-hand column, line 13 - page 54, left-hand column, line 56 page 57, left-hand column, line 14 - page 57, right-hand column, line 39	1,2, 5-10,12, 14,22-27

3

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/US2005/015018

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
US 6110485	A	29-08-2000	NONE			
US 6001386	A	14-12-1999	AT	284179	T	15-12-2004
			AU	717209	B2	23-03-2000
			AU	7371896	A	17-04-1997
			CA	2230947	A1	03-04-1997
			DE	69634009	D1	13-01-2005
			EP	0863729	A1	16-09-1998
			ES	2233981	T3	16-06-2005
			JP	11512711	T	02-11-1999
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